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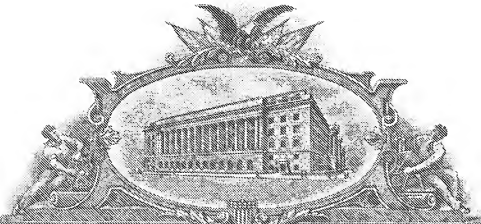

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APPLICATION NUMBER: ***60/532,546***
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Certified by

Jon W. Dudas

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COVER SHEET FOR PROVISIONAL APPLICATION FOR PATENT

Commissioner for Patents
P.O. Box 1450
Mail Stop Provisional Patent Application
Alexandria, VA 22313-1450

Sir:

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number	11151-026-888	Type a plus sign (+) inside this box 6	+

INVENTOR(s) APPLICANT(s)

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TITLE OF THE INVENTION (280 characters max)

NOVEL SPIROINDOLINE OR SPIROISOQUINOLINE COMPOUNDS, METHODS OF USE AND COMPOSITIONS THEREOF

PENNIE & EDMONDS LLP
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ENCLOSED APPLICATION PARTS (*check all that apply*)

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☐ A check or money order is enclosed to cover the Provisional filing fees.	ESTIMATED PROVISIONAL FILING FEE AMOUNT ☒ $160 ☐ $80
☒ The Commissioner is hereby authorized to charge the required filing fee to Deposit Account Number 16-1150.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
☒ No. ☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Signature Anthony M. Insogna, Reg. No. 35,203
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REGISTRATION NO. 35,203

Date December 23, 2003

☐ Additional inventors are being named on separately numbered sheets attached hereto.

Total number of cover sheet pages. 134

PROVISIONAL APPLICATION FILING ONLY

NOVEL SPIROINDOLINE OR SPIROISOQUINOLINE COMPOUNDS, METHODS OF USE AND COMPOSITIONS THEREOF

1. Field of the Invention

The present invention relates to novel Spiroindoline and Spiroisoquinoline Compounds and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, which are useful for example as cardio-protective or neuro-protective agents in mammals. The invention also encompasses compositions comprising a Spiroindoline or Spiroisoquinoline Compound and methods for treating or preventing diseases or disorders comprising the administration of a Spiroindoline or Spiroisoquinoline Compound to a patient in need thereof. Such diseases or disorders include cardiovascular diseases or disorders such as atherosclerosis, reperfusion injury, acute myocardial infarction, high blood pressure, primary or secondary hypertension, renal vascular hypertension, acute or chronic congestive heart failure, left ventricular hypertrophy, vascular hypertrophy, glaucoma, primary or secondary hyperaldosteronism, diabetic neuropathy, glomerulonephritis, scleroderma, glomerular sclerosis, renal failure, renal transplant therapy, diabetic retinopathy, and other vascular diseases or disorders such as migraine, and neurodegenerative diseases or disorders such as diabetic peripheral neuropathy, stroke, cerebral ischemia and Parkinson's disease.

2. Background of the Invention

G protein-coupled receptors (GPCRs) share the common structural motif of having seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the cell membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus residing in the extracellular space. It is thought that the loop joining helices five and six, as well as the carboxy terminus, interact with

the G protein. Currently, the G proteins that have been identified are Gq, Gs, Gi, and Go.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Change of the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response. Physiologically, these conformational changes are induced in response to binding of a molecule to the receptor. Several types of biological molecules can bind to specific receptors, such as peptides, hormones or lipids, and can cause a cellular response. Modulation of particular cellular responses can be extremely useful for the treatment of disease states, and a number of chemical agents that act on GPCRs are useful for the treatment of disease.

The *Mas* protooncogene encodes a GPCR protein (Mas) and was first detected *in vivo* by its tumorogenic properties which originate from rearrangement of its 5' flanking region (Young, D. *et al. Cell 45*:711-719 (1996)). Subsequent studies have indicated that the tumorogenic properties of Mas appear to be negligible and the lack of an activating ligand for Mas has made definition of its biological role difficult. A recent report that the biologically relevant angiotesin fragment Ang (1-7) (H-Asp-Arg-Val-Tyr-Ile-His-Pro-OH) is a ligand for Mas (Santos, R.A.S. *et al., PNAS 100(14)*:8258-8263 (2003)) has helped to define the role of Mas in blood pressure regulation and thrombus production.

The renin/angiotensin system is one of the major pathways by which blood pressure is regulated. Renin is produced in the kidneys in response to decrease in renal perfusion pressure when catecholamines or angiotensin II are present, or when sodium or chloride ion concentrations in the blood decline. Renin catalyzes the conversion of angiotensinogen to its inactive metabolite, angiotensin I. Angiotensin converting enzyme catalyzes the conversion of angiotensin I to angiotensin II, a powerful vasoconstrictor which acts on the angiotesin II receptor. The cardiovascular and baroreflex actions of Ang (1-7) counteract those of angiotensin II. Whereas, angiotensin II, acting at the AT_2 receptor causes vasoconstriction and concurrent increase in blood

pressure, Ang (1-7) acting at the Mas receptor causes vasodilation and blood pressure decrease.

The standard treatment for myocardial infarction is reperfusion of the ischemic area by thrombolysis or percutaneous coronary angioplasty. Release of the blockage and return of blood flow to the affected area is crucial for heart tissue survival; however, damage beyond that generated by ischemia is typically observed in the reperfused heart tissue. The manifestations of reperfusion injury include arrhythmia, reversible contractile dysfunction-myocardial stunning, endothelial dysfunction and cell death. Currently, there is no effective treatment for reperfusion injury available. Ang (1-7) has been shown to improve post-ischemic myocardial function in an ischmeia/reperfusion model using isolated rat hearts. (Ferreira, A. J. *et al.*, *Braz. J. of Med. and Biol. Res. 35(9)*:1083-1090 (2002).

In addition to the immediate adverse effects of myocardial infarction, subsequent loss of contractile function, scarring and tissue remodeling often lead to congestive heart failure (CHF). A follow-up to the Framingham Heart Study indicates that 22% of male and 46% of female myocardial infarction victims will be disabled with CHF within six years following their heart attack. Despite significant advances in the treatment and prevention of congestive heart disease, the prognosis for patients with CHF remains poor. A recent study reported that 12% of patients die within three months of diagnosis, 33% die within one year and approximately 60% die within five years.

Hypertension is the most common factor contributing to CHF. The American Heart Association estimates that 75% of CHF cases have antecedent hypertension. In most hypertensive individuals, cardiac output is normal but there is an increase in resistance in the arteriole circulation causing the heart to pump harder to overcome the peripheral resistance and perfuse the peripheral tissues. The left ventricle develops pressure hypertrophy, which leads to myocardial remodeling and reduced pumping capacity resulting in a cycle of reduced cardiac function. Control of blood pressure is an effective treatment for chronic CHF and considerable effort has been focused on the development of therapies for hypertension. Foremost among these, are the angiotensin converting enzyme inhibitors (ACEIs). ACEIs block the conversion of angiotensin I to angiotensin II, thus, decreasing the hypertensive effects resulting from angiotensin II.

Additionally, beta blockers, which act on the beta adrenergic receptor and inhibit sympathetic innervation of the heart, are used to treat chronic hypertension. Although these therapies are effective, there can be severe side effects associated with their use. As such, they are not tolerated by all individuals and the there is a need for new and effective alternatives to these therapies.

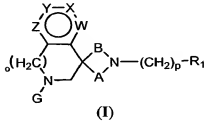
Ang (1-7) has a vasodilatory effect in many vascular beds, including canine and porcine coronary arteries, rat aorta, and feline mesenteric arteries. Chronic infusion of Ang (1-7) in spontaneously hypertensive rats and Dahl salt-sensitive rats has been shown to reduce mean arterial blood pressure. Ang (1-7) blocks the Ang II induced vasoconstriction in isolated human arteries and antagonized vasoconstriction in forearm circulation by Ang II in normotensive men. Direct vasodilation to the same extent in basal forearm circulation of both normotensive and hypertensive patients by Ang (1-7) has been observed. Additionally, although the mechanism is undefined, it is believed that the vasodilation effects of bradykinin are potentiated by Ang (1-7).

The discovery that Ang (1-7) is an endogenous ligand for the Mas receptor has provided validation of the importance of the development of therapeutic entities which modulate Mas receptor activity. However, the inherent instability of Ang (1-7) and the likelihood that it is not absorbed upon oral administration make it ineffective as a therapeutic agent. These considerations highlight the importance of the development of stable small molecule modulators of the Mas receptor for the safe and effective treatment and/or prevention of human diseases.

Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application.

3. Summary of the Invention

The present invention encompasses Spiroindoline and Spiroisoquinoline Compounds of Formula (I):



(I)

and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, wherein:

R_1 is H, halogen, hydroxy, nitro, cyano, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle, substituted or unsubstituted -(5 to 10) membered heteroaryl, $-NR_2R'_2$, $-C(=O)-R_7$, $-S(=O)_2-R_7$;

A is substituted or unsubstituted C_1-C_3 alkylene;

B is substituted or unsubstituted C_1-C_3 alkylene;

G is H, -Ar, $-C(=O)$-Ar, $-C(=O)O$-Ar, $-C(=O)O-C_{1-6}$ alkyl, $-C(=O)N(R_7)$(Ar), $-C(=O)N(R_7)(C_{1-6}$ alkyl), $-S(=O)_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or $-C(=O)C_{1-6}$ alkyl-Ar;

W is N or $-CR_3-$;

X is N or $-CR_4-$;

Y is N or $-CR_5-$;

Z is N or $-CR_6-$;

R_2, R_2', R_3, R_4, R_5, R_6 and R_7 are at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted

or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, -C(=O)-O-C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{0-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{0-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{0-6} alkyl-O-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-NR'-S(=O)$_2$-R', -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$;

o is 0 or 1;

p is 0, 1 or 2;

R' is at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_{3-8} cycloalkyl; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl.

The compounds of Formula (I) are further described below.

The invention also relates to radio-labeled compounds of Formula (I) including, but not limited to, those containing one or more ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I or ^{131}I atoms.

Spiroindoline and Spiroisoquinoline compounds of Formula (I) or pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof ("Compound(s) of the Invention"), are useful as a cardio-protective and/or neuroprotective agents. The Compounds of the Invention are also useful for treating, preventing and/or managing cardiovascular diseases or disorders including, but not limited to, atherosclerosis, reperfusion injury, acute myocardial infarction, high

blood pressure, hypertension, primary or secondary hypertension, renal vascular hypertension, acute or chronic congestive heart failure, left ventricular hypertrophy, vascular hypertrophy, glaucoma, primary or secondary hyperaldosteronism, diabetic neuropathy, glomerulonephritis, scleroderma, glomerular sclerosis, renal failure, renal transplant therapy, diabetic retinopathy, other vascular diseases or disorders and migraines. A Compound of the Invention is also useful for treating, preventing and/or managing neurodegenerative diseases or disorders including, but not limited to, diabetic peripheral neuropathy, stroke, cerebral ischemia and Parkinson's disease in a patient in need thereof. The Compounds of the Invention can also be used in patients at risk of such diseases and disorders as cardio-protective or neuro-protective agents.

In another embodiment, the Compounds of the Invention are used in combination with, or in place of, angiotensin-converting enzyme (ACE) inhibitors to treat the diseases or disorders for which such ACE inhibitors are conventionally used.

The invention further relates to methods for assaying the ability of a Compound of the Invention or another compound to bind to a Mas receptor, comprising contacting a radio-labeled Compound of the Invention with a cell capable of expressing a Mas receptor.

The invention further relates to compositions comprising a Compound of the Invention and a pharmaceutically acceptable vehicle or excipient. The compositions are useful as cardio-protective and/or neuro-protective agents and for treating or preventing a cardiovascular disorder and/or a neurodegenerative disorder in a patient.

The invention further relates to methods for treating a cardiovascular disorder and/or a neurodegenerative disorder, comprising administering to a patient in need thereof a Compound of the Invention.

The invention further relates to methods for preventing a cardiovascular disorder and/or a neurodegenerative disorder, comprising administering to a patient in need thereof a Compound of the Invention.

The invention further relates to methods for managing a cardiovascular disorder and/or a neurodegenerative disorder, comprising administering to a patient in need thereof a Compound of the Invention.

The invention further relates to methods for inhibiting Mas function in a cell, comprising contacting a cell capable of expressing Mas with a Compound of the Invention.

The invention further relates to a method for manufacturing a medicament, comprising the step of admixing a Compound of the Invention and a pharmaceutically acceptable vehicle or excipient. In a particular embodiment, a medicament comprising a Compound of the Invention is useful for treating, preventing and/or managing a cardiovascular disorder and/or a neurodegenerative disorder. In another embodiment, a medicament comprising a Compound of the Invention is useful as a cardio-protective or neuro-protective agent.

The invention further relates to a Compound of the Invention, as described herein, for use in a method of treatment of the human or animal body by therapy.

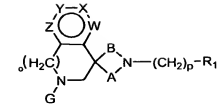
The invention still further relates to a kit comprising a container containing a Compound of the Invention. The kit may further comprise printed instructions for using the Compound of the Invention to treat, prevent and/or manage any of the aforementioned diseases or disorders.

The present invention may be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

4. Detailed Description of the Invention

4.1 Spiroindoline and Spiroisoquinoline Compounds of Formula (I)

The present invention encompasses Spiroindoline and Spiroquinoline Compounds of Formula (I):



(I)

and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, wherein A, B, G, W, X, Y, Z, o, p and R_1 are defined above ("Compound(s) of the Invention").

In one embodiment, W, X, Y and Z are each -CH-.

In another embodiment, W, Y and Z are each -CH- and X is -C(halogen)-.

In another embodiment, W, Y and Z are each -CH- and X is -C(Cl)- or -C(F)-.

In another embodiment, W, Y and Z are each -CH- and X is $-C(CH_3)-$, $-C(OCH_3)-$, -C(OH)-, $-C(OS(=O)_2CH_3)-$ or $-C(CF_3)-$.

In another embodiment, W, X and Z are each -CH- and Y is -C(F)- or -C(Cl)-.

W and Y may also each be -CH- while X and Z are substituted carbon atoms. Preferably, X and Z are substituted with lower alkyl, halogen, hydroxy or lower alkoxy. Most preferably, W and Y are each -CH- and X and Z are each $-C(CH_3)-$ or $-C(CF_3)-$.

Another subclass is formed wherein A and B are each $-(CH_2)_2-$ or one of A and B is $-(CH_2)_2-$ and the other is $-(CH_2)-$.

In another embodiment, p is 1 or 2 and R_1 is $-CH=CH_2$.

In another embodiment, p is 1 or 2 and R_1 is -cyclopropyl.

In another embodiment, p is 1 and R_1 is $-CH_2CH_3$.

In another embodiment, p is 1 and R_1 is $-(CH_2)_2CH_3$.

In another embodiment, p is 0 and R_1 is phenyl.

In another embodiment, p is 1 or 2 and R_1 is phenyl.

In another embodiment, p is 1 and R_1 is $-CH(OH)CH_3$.

In another embodiment, p is 1 and R_1 is $-C(=CH_2)CH_3$.

In another embodiment, p is 1 and R_1 is H.

In another embodiment, p is 0 and R_1 is H.

In another embodiment, G is -C(=O)-Ar.

In another embodiment, G is $-C(=O)CH_2-Ar$ or G is $-C(=O)CH(Ar)_2$.

In another embodiment, G is $-C(=O)NH-Ar$ or $-C(=O)NH_2$ or $-C(=O)NH(alkyl)$.

In another embodiment, G is $-S(=O)_2-Ar$.

In another embodiment, Ar is substituted or unsubstituted phenyl; preferably mono or disubstituted phenyl; most preferably mono or disubstituted phenyl substituted with either halogen, lower alkyl or lower alkoxy.

In another embodiment, Ar is methoxy phenyl substituted in the para position.

In another embodiment, Ar is fluorophenyl substituted in the ortho position.

In another embodiment, Ar is fluorophenyl substituted in the para position.

In another embodiment, Ar is difluorophenyl substituted in the ortho and para positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho and meta positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho positions.

In another embodiment, Ar is difluorophenyl substituted in the meta positions.

In another embodiment, Ar is substituted or unsubstituted furan.

In another embodiment, Ar is substituted or unsubstituted pyridine.

In another embodiment, Ar is substituted or unsubstituted thiophene.

In another embodiment, Ar is substituted or unsubstituted adamantane.

In another embodiment, Ar is 2-chlorothiophene.

In another embodiment, Ar is benzo(1,3)dioxole.

In another embodiment, Ar is fluoren-9-one.

In another embodiment, Ar is morpholine.

In another embodiment, o is 0. In another specific embodiment, when o is 1, another subclass of compounds is formed.

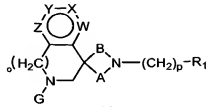
In another embodiment, p is 0. In another specific embodiment, when p is 1, another subclass of compounds is formed.

In another embodiment, when X is -C(F)-, then G is preferably -C(=O)-substituted or unsubstituted phenyl.

In another embodiment, when X is -C(F)-, then G is preferably -C(=O)-substituted or unsubstituted -(3 to 7) membered heterocycle.

In another embodiment, when X is -C(F)-, then G is preferably -C(=O)N-substituted or unsubstituted phenyl.

In another embodiment, the present invention encompasses compounds of Formula (I):



(I)

and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, wherein:

R_1 is H, halogen, hydroxy, nitro, cyano, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle, substituted or unsubstituted -(5 to 10) membered heteroaryl, $-NR_2R'_2$, $-C(=O)-R_7$, $-S(=O)_2-R_7$;

wherein the foregoing when substituted can be independently substituted with one or more substituents selected from $-C(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$O-C_{1-6}$ alkyl, $-C_{0-6}$ alkyl-$C(=O)-NH(C_{1-6}$ alkyl), $-C_{0-6}$ alkyl-$C(=O)-N(C_{1-6}$ alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-$NH-C(=O)-C_{1-6}$ alkyl, $-C_{0-6}$ alkyl-$C(=S)-NH(C_{1-6}$ alkyl), $-C_{0-6}$ alkyl-$C(=S)-N(C_{1-6}$ alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-$NH-C(=S)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$S(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$S(=O)_2-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-SH, $-C_{1-6}$ alkyl-$S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$NH-C(=S)-NH-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$NH-C(=O)-NH-C_{1-6}$ alkyl, $-C_{0-6}$ alkyl-$N(R')_2$, $-C_{0-6}$ alkyl-NHOH, $-C_{0-6}$ alkyl-$C(=O)O-C_{1-6}$ alkyl, $-C_{0-6}$ alkyl-$C(=O)OH$, $-(C(R')_2)_{0-6}-O-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}-S-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}-S(=O)-(C(R')_2)_{1-5}C(R')_3$ or $-(C(R')_2)_{0-6}-S(=O)_2-(C(R')_2)_{1-5}C(R')_3$;

A is substituted or unsubstituted C_{1-3} alkylene;

B is substituted or unsubstituted C_{1-3} alkylene;

G is H, -Ar, -C(=O)-Ar, -C(=O)O-Ar, -C(=O)O-C_{1-6} alkyl, -C(=O)N(R_7)(Ar), -C(=O)N(R_7)(C_{1-6} alkyl), -S(=O)$_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or -C(=O)C_{1-6} alkyl-Ar;

W is N or -CR_3-;

X is N or -CR_4-;

Y is N or -CR_5-;

Z is N or -CR_6-;

R_2, R_2', R_3, R_4, R_5, R_6 and R_7 are at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, -C(=O)-O-C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{0-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{0-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{0-6} alkyl-O-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$,

wherein when each C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-8} cycloalkyl is substituted, it can be individually substituted with one or more substituents selected from amino, carboxy, cyano, halogen, hydroxyl, nitro, -C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{1-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl(=S)-NH(C_{1-6} alkyl), -C_{1-6} alkyl-C(=S)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=S)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -C_{1-6} alkyl-C(=O)OH, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$;

o is 0 or 1;

p is 0, 1 or 2;

R' is at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_{3-8} cycloalkyl; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl,

wherein when the foregoing is substituted, each is substituted with one or more substituents selected from cyano, halogen, hydroxyl, nitro, -(3- to 7-membered heterocycle), -(5- to 10 membered)heteroaryl, -O-phenyl, phenyl, $-SO_3H$, C_{1-8} alkyl, $-C(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C_{1-6}$ alkyl-$C(=O)$-NH(C_{1-6} alkyl), $-C_{1-6}$ alkyl-$C(=O)$-N(C_{1-6} alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-NH-$C(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl$(=S)$-NH(C_{1-6} alkyl), $-C_{1-6}$ alkyl$(=S)$-N(C_{1-6} alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-NH-$C(=S)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$S(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$S(=O)_2-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-SH, $-C_{1-6}$ alkyl-S-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-$C(=S)$-NH-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-$C(=O)$-NH-C_{1-6} alkyl, $-C_{0-6}$ alkyl-N(R')$_2$, $-C_{0-6}$ alkyl-NHOH, $-C_{1-6}$ alkyl-$C(=O)O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl$(=O)$OH, $-(C(R')_2)_{0-6}-O-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}-S-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}-S(=O)-(C(R')_2)_{1-5}C(R')_3$ or $-(C(R')_2)_{0-6}-S(=O)_2-(C(R')_2)_{1-5}C(R')_3$;

wherein each of the above substituents can be further substituted with one or more substituents independently selected from cyano, halogen, hydroxyl, nitro, -(3 to 7 membered heterocycle), -(5 to 10 membered)heteroaryl, -O-phenyl, phenyl, $-SO_3H$, $-C(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C_{1-6}$ alkyl-$C(=O)$-NH(C_{1-6} alkyl), $-C_{1-6}$ alkyl-$C(=O)$-N(C_{1-6} alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-NH-$C(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl$(=S)$-NH(C_{1-6} alkyl), $-C_{1-6}$ alkyl$(=S)$-N(C_{1-6} alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-NH-$C(=S)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$S(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$S(=O)_2-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-SH, $-C_{1-6}$ alkyl-S-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-$C(=S)$-NH-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-$C(=O)$-NH-C_{1-6} alkyl, $-C_{0-6}$ alkyl-N(R')$_2$, $-C_{0-6}$ alkyl-NHOH, $-C_{1-6}$ alkyl-$C(=O)O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$C(=O)$OH, $-(C(R')_2)_{0-6}-O-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}-S-(C(R')_2)_{1-}$

$_5C(R')_3$, $-(C(R')_2)_{0-6}-S(=O)-(C(R')_2)_{1-5}C(R')_3$ or $-(C(R')_2)_{0-6}-S(=O)_2-(C(R')_2)_{1-5}C(R')_3$, or two adjacent substituents together with said aryl or -(5- to 10-membered)heteroaryl form a (C_{3-8}) cycloalkyl, (C_{5-10}) cycloalkenyl or -(3- to 7-membered) heterocyclic group may optionally substituted with one or more halogens.

In another embodiment, the present invention encompasses compounds of Formula (I), wherein:

A, B, W, X, Y, Z, o, p and R_1 are as defined above;

G is H, -Ar, -C(=O)O-Ar, -C(=O)O-C_{1-6} alkyl, -C(=O)N(R_7)(Ar), -C(=O)N(R_7)(C_{1-6} alkyl), $-S(=O)_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or -C(=O)C_{1-6} alkyl-Ar; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl,

wherein when the foregoing is substituted, each is substituted with one or more substituents selected from cyano, halogen, hydroxyl, nitro, -(3- to 7-membered heterocycle), -(5- to 10 membered)heteroaryl, -O-phenyl, phenyl, $-SO_3H$, C_{1-8} alkyl, -C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{1-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH(C_{1-6} alkyl), -C_{1-6} alkyl(=S)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=S)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-$S(=O)_2$-C_{1-6} alkyl, -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{1-6} alkyl-C(=O)O-C_{1-6} alkyl, -C_{1-6} alkyl(=O)OH, $-(C(R')_2)_{0-6}-O-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}-S-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}-S(=O)-(C(R')_2)_{1-5}C(R')_3$ or $-(C(R')_2)_{0-6}-S(=O)_2-(C(R')_2)_{1-5}C(R')_3$;

wherein each of the above substituents can be further substituted with one or more substituents independently selected from cyano, halogen, hydroxyl, nitro, -(3 to 7 membered heterocycle), -(5 to 10 membered)heteroaryl, -O-phenyl, phenyl, $-SO_3H$, -C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{1-6} alkyl-

C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl(=S)-NH(C_{1-6} alkyl), -C_{1-6} alkyl(=S)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=S)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{1-6} alkyl-C(=O)O-C_{1-6} alkyl, -C_{1-6} alkyl-C(=O)OH, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$, or two adjacent substituents together with said aryl or -(5- to 10-membered)heteroaryl form a (C_{3-8}) cycloalkyl, (C_{5-10}) cycloalkenyl or -(3- to 7-membered) heterocyclic group may optionally substituted with one or more halogens.

In another embodiment, the present invention encompasses compounds of Formula (I), wherein:

A, B, G, W, X, Y, Z, o, p and R_1 are as defined above;

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl,

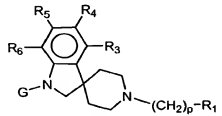
wherein when the foregoing is substituted, each is substituted with one or more substituents selected from cyano, halogen, hydroxyl, nitro, -(3- to 7-membered heterocycle), -(5- to 10 membered)heteroaryl, -O-phenyl, phenyl, -SO_3H, C_{1-8} alkyl, -C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{1-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl(=S)-NH(C_{1-6} alkyl), -C_{1-6} alkyl(=S)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=S)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{1-6} alkyl-C(=O)O-C_{1-6} alkyl, -C_{1-6} alkyl(=O)OH, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$;

wherein each of the above substituents can be further substituted with one or more substituents independently selected from cyano, halogen, hydroxyl, nitro, -(3 to 7 membered heterocycle), -(5 to 10 membered)heteroaryl, -O-phenyl, phenyl, $-SO_3H$, $-C(=O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C_{1-6}$ alkyl-C(=O)-NH(C_{1-6} alkyl), $-C_{1-6}$ alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-NH-C(=O)-C_{1-6} alkyl, $-C_{1-6}$ alkyl(=S)-NH(C_{1-6} alkyl), $-C_{1-6}$ alkyl(=S)-N(C_{1-6} alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-NH-C(=S)-C_{1-6} alkyl, $-C_{1-6}$ alkyl-S(=O)-C_{1-6} alkyl, $-C_{1-6}$ alkyl-S(=O)$_2$-C_{1-6} alkyl, $-C_{1-6}$ alkyl-SH, $-C_{1-6}$ alkyl-S-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-C(=S)-NH-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-C(=O)-NH-C_{1-6} alkyl, $-C_{0-6}$ alkyl-N(R')$_2$, $-C_{0-6}$ alkyl-NHOH, $-C_{1-6}$ alkyl-C(=O)O-C_{1-6} alkyl, $-C_{1-6}$ alkyl-C(=O)OH, $-(C(R')_2)_{0-6}$-O-$(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}$-S-$(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}$-S(=O)-$(C(R')_2)_{1-5}C(R')_3$ or $-(C(R')_2)_{0-6}$-S(=O)$_2$-$(C(R')_2)_{1-5}C(R')_3$, or two adjacent substituents together with said aryl or -(5- to 10-membered)heteroaryl form a (C_{3-8}) cycloalkyl, (C_{5-10}) cycloalkenyl or -(3- to 7-membered) heterocyclic group may optionally substituted with one or more halogens; and

when X is $-CR_4-$, R_4 is H, hydroxy, amino, cyano, nitro, Br, Cl, C_1-C_7 alkyl substituted with halogen, substituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, $-C(=O)-O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C_{1-6}$ alkyl-C(=O)-NH(C_{1-6} alkyl), $-C_{1-6}$ alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-NH-C(=O)-C_{1-6} alkyl, $-C_{1-6}$ alkyl-S(=O)-C_{1-6} alkyl, $-C_{1-6}$ alkyl-S(=O)$_2$-C_{1-6} alkyl, $-C_{1-6}$ alkyl-SH, $-C_{1-6}$ alkyl-S-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-C(=S)-NH-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH-C(=O)-NH-C_{1-6} alkyl, $-C_{0-6}$ alkyl-N(R')$_2$, $-C_{0-6}$ alkyl-NHOH, $-C_{1-6}$ alkyl-C(=O)O-C_{1-6} alkyl, $-(C(R')_2)_{0-6}$-O-$(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}$-S-$(C(R')_2)_{1-5}C(R')_3$, $-(C(R')_2)_{0-6}$-S(=O)-$(C(R')_2)_{1-5}C(R')_3$ or $-(C(R')_2)_{0-6}$-S(=O)$_2$-$(C(R')_2)_{1-5}C(R')_3$.

4.2 Compounds of the Invention of Formula (II)

In one embodiment, the Compounds of the Invention are those where W, X, Y and Z are $-CR_3$, $-CR_4$, $-CR_5$ and $-CR_6$, respectively; o is 0; and A and B are both unsubstituted $-(CH_2)_2-$ as set forth in Formula (II):



(II)

and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, where G, R_1, R_3, R_4, R_5, R_6 and p are as defined above for the compounds of Formula (I).

In one embodiment, p is 1 or 2 and R_1 is $-CH=CH_2$.

In another embodiment, p is 1 or 2 and R_1 is -cyclopropyl.

In another embodiment, p is 1 or 2 and R_1 is $-CH_2CH_3$.

In another embodiment, p is 1 or 2 and R_1 is $-(CH_2)_2CH_3$.

In another embodiment, p is 0 or 1 and R_1 is substituted or unsubstituted phenyl.

In another embodiment, p is 1 and R_1 is $-CH(OH)CH_3$.

In another embodiment, p is 1 and R_1 is $-C(=CH_2)CH_3$.

In another embodiment, p is 1 and R_1 is H.

In another embodiment, G is -C(=O)-Ar, -C(=O)NH-Ar or $-C(=O)NR_8R_8'$ wherein R_8 and R_8' taken together with the nitrogen to which they are attached form a 3 to 7 membered heterocyclic or heteroaromatic ring having one or more nitrogen, oxygen or sulfur atoms. Preferred groups are morphilino, pyrrolidano, piperidino or imidazolino rings which can be substituted or unsubstituted.

In another embodiment, G is $-C(=O)CH_2$-Ar.

In another embodiment, G is $-C(=O)CH-(Ar)_2$.

In another embodiment, G is -C(=O)NH-(Ar).

In another embodiment, G is $-S(=O)_2$-Ar.

In another embodiment, Ar is substituted or unsubstituted phenyl. Preferably Ar is mono or disubstituted phenyl wherein the substituents are selected from halogen, lower alkyl, lower alkenyl, lower alkoxy and C_{3-7} cycloalkyl.

In another embodiment, Ar is methoxy phenyl substituted in the para position.

In another embodiment, Ar is fluorophenyl substituted in the ortho position.

In another embodiment, Ar is fluorophenyl substituted in the para position.

In another embodiment, Ar is difluorophenyl substituted in the ortho and para positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho and meta positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho positions.

In another embodiment, Ar is difluorophenyl substituted in the meta positions.

In another embodiment, Ar is substituted or unsubstituted furan.

In another embodiment, Ar is substituted or unsubstituted pyridine.

In another embodiment, Ar is substituted or unsubstituted thiophene.

In another embodiment, Ar is substituted or unsubstituted adamantane.

In another embodiment, Ar is 2-chlorothiophene.

In another embodiment, Ar is benzo(1,3)dioxole.

In another embodiment, Ar is fluoren-9-one.

In another embodiment, Ar is morpholine.

In another embodiment, p is 0; and in another embodiment, p is 1.

In another embodiment, one or more of R_3-R_6 is a substituent other than H.

In another embodiment, two or more of R_3-R_6 is a substituent other than H.

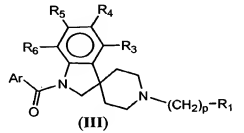
In another embodiment, three or more of R_3-R_6 is a substituent other than H.

In another embodiment, each of R_3-R_6 is a substituent other than H.

Preferred R_3-R_6 groups include halogen, preferably fluoro or chloro; -C_{1-6} alkyl, preferably methyl; -O-C_{1-6} alkyl, preferably methoxy; and hydroxy.

4.3 Compounds of the Invention of Formula (III)

In one embodiment, the Compounds of the Invention are those where W, X, Y and Z are $-CR_3$, $-CR_4$, $-CR_5$ and $-CR_6$, respectively; o is 0; A and B are both unsubstituted $-(CH_2)_2-$; and G is -C(=O)-Ar as set forth in Formula (III):



(III)

and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, where Ar, R_1, R_3, R_4, R_5, R_6 and p are as defined above for the Compounds of the Invention of Formula (I).

In one embodiment, p is 1 and R_1 is C_{2-6} alkenyl, preferably $-CH=CH_2$.

In another embodiment, p is 1 and R_1 is C_3-C_7 cycloalkyl, preferably -cyclopropyl.

In another embodiment, p is 1 and R_1 is C_{1-6} alkyl, preferably $-CH_2CH_3$.

In another embodiment, p is 1 and R_1 is C_{1-6} alkyl, preferably $-(CH_2)_2CH_3$.

In another embodiment, p is 0 and R_1 is substituted or unsubstituted phenyl.

In another embodiment, p is 1 and R_1 is $-CH(OH)CH_3$.

In another embodiment, p is 1 and R_1 is $-C(=CH_2)CH_3$.

In another embodiment, p is 0 and R_1 is H.

In another embodiment, p is 1 and R_1 is H.

In another embodiment, Ar is substituted or unsubstituted phenyl, substituted or unsubstituted naphthalene, substituted or unsubstituted thiophene, substituted or unsubstituted pyrindine, pyrazole, pyrrole, quinazoline, pyrazine or quinoline.

In another embodiment, Ar is methoxy phenyl substituted in the para position.

In another embodiment, Ar is fluorophenyl substituted in the ortho position.

In another embodiment, Ar is fluorophenyl substituted in the para position.

In another embodiment, Ar is difluorophenyl substituted in the ortho and para positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho and meta positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho positions.

In another embodiment, Ar is difluorophenyl substituted in the meta positions.

In another embodiment, Ar is substituted or unsubstituted furan.

In another embodiment, Ar is substituted or unsubstituted pyridine.

In another embodiment, Ar is substituted or unsubstituted thiophene.

In another embodiment, Ar is substituted or unsubstituted adamantane.

In another embodiment, Ar is 2-chlorothiophene.

In another embodiment, Ar is benzo(1,3)dioxole.

In another embodiment, Ar is fluoren-9-one.

In another embodiment, Ar is morpholine.

In another embodiment, p is 0; and in another embodiment, p is 1.

In another embodiment, one or more of R_3-R_6 is a substituent other than H.

In another embodiment, two or more of R_3-R_6 is a substituent other than H.

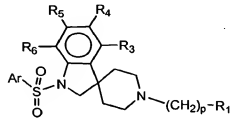
In another embodiment, three or more of R_3-R_6 is a substituent other than H.

In another embodiment, each of R_3-R_6 is a substituent other than H.

Preferred R_3-R_6 groups include halogen, preferably fluoro or chloro; -C_{1-6} alkyl, preferably methyl; and -O-C_{1-6} alkyl, preferably methoxy.

4.4 Compounds of the Invention of Formula (IV)

In one embodiment, the Compounds of the Invention are those where W, X, Y and Z are $-CR_3$, $-CR_4$, $-CR_5$ and $-CR_6$, respectively; o is 0; A and B are both unsubstituted $-(CH_2)_2-$; and G is $-S(=O)_2-Ar$ as set forth in Formula (IV):



(IV)

and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, where Ar, R_1, R_3, R_4, R_5, R_6 and p are as defined above for the Compounds of the Invention of Formula (I).

In one embodiment, p is 1 and R_1 is C_{2-6} alkenyl, preferably $-CH=CH_2$.

In another embodiment, p is 1 and R_1 is C_3-C_7 cycloalkyl, preferably -cyclopropyl.

In another embodiment, p is 1 and R_1 is C_{1-6} alkyl, preferably $-CH_2CH_3$.

In another embodiment, p is 1 and R_1 is C_{1-6} alkyl, preferably $-(CH_2)_2CH_3$.

In another embodiment, p is 0 and R_1 is substituted or unsubstituted phenyl.

In another embodiment, p is 1 and R_1 is $-CH(OH)CH_3$.

In another embodiment, p is 1 and R_1 is $-C(=CH_2)CH_3$.

In another embodiment, p is 1 and R_1 is H.

In another embodiment, p is 0 and R_1 is H.

In another embodiment, Ar is substituted or unsubstituted phenyl.

In another embodiment, Ar is methoxy phenyl substituted in the para position.

In another embodiment, Ar is fluorophenyl substituted in the ortho position.

In another embodiment, Ar is fluorophenyl substituted in the para position.

In another embodiment, Ar is difluorophenyl substituted in the ortho and para positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho and meta positions.

In another embodiment, Ar is difluorophenyl substituted in the ortho positions.

In another embodiment, Ar is difluorophenyl substituted in the meta positions.

In another embodiment, Ar is substituted or unsubstituted furan.

In another embodiment, Ar is substituted or unsubstituted pyridine.

In another embodiment, Ar is substituted or unsubstituted thiophene.

In another embodiment, Ar is substituted or unsubstituted adamantane.

In another embodiment, Ar is 2-chlorothiophene.

In another embodiment, Ar is benzo(1,3)dioxole.

In another embodiment, Ar is fluoren-9-one.

In another embodiment, Ar is morpholine.

In another embodiment, p is 0; and in another embodiment, p is 1.

In another embodiment, one or more of R_3-R_6 is a substituent other than H.

In another embodiment, two or more of R_3-R_6 is a substituent other than H.

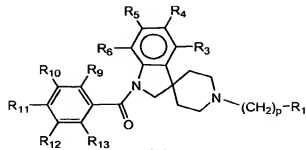
In another embodiment, three or more of R_3-R_6 is a substituent other than H.

In another embodiment, each of R_3-R_6 is a substituent other than H.

Preferred R_3-R_6 groups include halogen, preferably fluoro or chloro; -C_{1-6} alkyl, preferably methyl; and -O-C_{1-6} alkyl, preferably methoxy.

4.5 Compounds of the Invention of Formula (V)

In one embodiment, the Compounds of the Invention are those where W, X, Y and Z are -CR_3, -CR_4, -CR_5 and -CR_6, respectively; o is 0; A and B are both unsubstituted -$(CH_2)_2$-; and G is -C(=O)-Ar as set forth in Formula (V):



(V)

and pharmaceutically acceptable salts, free bases, solvates, hydrates, stereoisomers, clathrates or prodrugs thereof, where R_1, R_3, R_4, R_5, R_6 and p are as defined above for the Compounds of the Invention of Formula (I), and R_9-R_{13} are each independently H, halogen, nitro, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted -O-C_{1-6} alkyl or R_{10} and R_{11} taken together form -O-CH_2-O-.

In one embodiment, R_9-R_{13} are each H.

In another embodiment, R_{10}-R_{13} are H and R_9 is halogen, preferably fluoro or chloro.

In another embodiment, R_9, R_{10}, R_{12} and R_{13} are H and R_{11} is methoxy.

In another embodiment, R_9, R_{10}, R_{12} and R_{13} are H and R_{11} is nitro.

In another embodiment, R_9, R_{12} and R_{13} are H, R_{10} is nitro and R_{11} is methyl.

In another embodiment, R_9, R_{10}, R_{12} and R_{13} are H and R_{11} is halogen, preferably fluoro or chloro.

In one embodiment, R_{10}-R_{13} are H and R_9 is methoxy.

In another embodiment, R_9, R_{12} and R_{13} are H and R_{10} and R_{11} taken together form -O-CH_2-O-.

In another embodiment, R_9, R_{12} and R_{13} are H and R_{10} and R_{11} are each halogen, preferably fluoro or chloro.

In another embodiment, R_9, R_{10}, R_{12} and R_{13} are H and R_{11} is halogen, preferably fluoro or chloro.

In another embodiment, R_9, R_{11} and R_{13} are H, and R_{10} and R_{12} are each halogen, preferably fluoro or chloro.

In another embodiment, R_9, R_{11} and R_{13} are H, and R_{10} and R_{12} are each methoxy.

In another embodiment, R_9 and R_{11}-R_{13} are H, and R_{10} is halogen, preferably fluoro chloro.

In another embodiment, R_{11}-R_{13} are H and R_9 and R_{10} are each halogen, preferably fluoro or chloro.

In another embodiment, R_{10}, R_{12} and R_{13} are H and R_9 and R_{11} are each halogen, preferably fluoro or chloro.

In another embodiment, R_9 and R_{11}-R_{13} are H, and R_{10} is trifluoromethyl.

In another embodiment, R_9, R_{11} and R_{13} are H, and R_{10} and R_{12} are each trifluoromethyl.

In another embodiment, R_9 and R_{11}-R_{13} are H, and R_{10} is nitro.

In another embodiment, R_9, R_{12} and R_{13} are H, R_{10} is trifluoromethyl and R_{11} is halogen, preferably fluoro or chloro.

In another embodiment, R_9 and R_{11}-R_{13} are H, and R_{10} is dichloromethyl.

In another embodiment, R_9 and R_{13} are H, and R_{10}, R_{11} and R_{12} are each methoxy.

In another embodiment, R_{10}, R_{11} and R_{13} are H and R_9 and R_{12} are each halogen, preferably fluoro or chloro.

In another embodiment, R_{10}-R_{12} are H and R_9 and R_{13} are each halogen, preferably fluoro or chloro.

In another embodiment, R_{11}-R_{13} are H and R_9 and R_{10} are each halogen, preferably fluoro or chloro.

In another embodiment, p is 1 and R_1 is $C_{2\text{-}6}$ alkenyl, preferably $-CH{=}CH_2$.

In another embodiment, p is 1 and R_1 is $C_{3\text{-}7}$ cycloalkyl, preferably -cyclopropyl.

In another embodiment, p is 1 and R_1 is $C_{1\text{-}6}$ alkyl, preferably $-CH_2CH_3$.

In another embodiment, p is 1 and R_1 is $C_{1\text{-}6}$ alkyl, preferably $-(CH_2)_2CH_3$.

In another embodiment, p is 0 and R_1 is substituted or unsubstituted phenyl.

In another embodiment, p is 1 and R_1 is $-CH(OH)CH_3$.

In another embodiment, p is 1 and R_1 is $-C(=CH_2)CH_3$.

In another embodiment, p is 0 and R_1 is H.

In another embodiment, p is 1 and R_1 is H.

In another embodiment, one or more of R_3-R_6 is a substituent other than H.

In another embodiment, two or more of R_3-R_6 is a substituent other than H.

In another embodiment, three or more of R_3-R_6 is a substituent other than H.

In another embodiment, each of R_3-R_6 is a substituent other than H.

Preferred R_3-R_6 groups include halogen, preferably fluoro or chloro; -C_{1-6} alkyl, preferably methyl; and -O-C_{1-6} alkyl, preferably methoxy.

The invention also includes specific subclasses of the compounds of Formula I wherein G is -C(=O)-Ar, $(CH_2)_o$ is absent and X is -C(F)-, -$C(OCH_3)$- or -$C(CH_3)$-, then W, Y and Z are not all -CH-. Similarly, the invention encompasses, in another embodiment, a specific subclass of the compounds of Formula II wherein when G is -C(=O)-Ar and R_4 is -OCH_3, -F or -CH_3, then R_3, R_5 and R_6 are not all hydrogen. Finally, the invention includes a specific subclass of the compounds of Formula III wherein when R_4 is -F, -OCH_3 or -CH_3, then R_6, R_5 and R_3 are not all hydrogen, or p of -(CH_2)p- is not 1, or when p is 0, R_1 is not cycloalkyl or -CH_3.

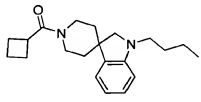
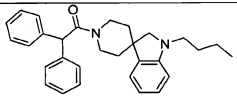
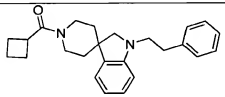
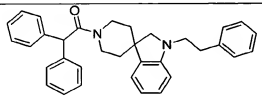
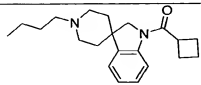
When the groups described herein are said to be "substituted or unsubstituted," when substituted, they may be substituted with any desired substituent or substituents that do not adversely affect the desired activity of the compound. Examples of preferred substituents are those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; hydroxyl; C_{1-6} alkoxyl; amino; nitro; thiol; thioether; imine; cyano; amido; phosphonato; phosphine; carboxyl; thiocarbonyl; sulfonyl; sulfonamide; ketone; aldehyde; ester; oxygen (=O); haloalkyl (*e.g.*, trifluoromethyl); carbocyclic cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocycloalkyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiazinyl); carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic aryl (*e.g.*, phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridinyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzothiophenyl, or benzofuranyl); amino (primary, secondary, or tertiary); o-lower alkyl; o-aryl, aryl; aryl-lower alkyl; CO_2CH_3; $CONH_2$; OCH_2CONH_2; NH_2; SO_2NH_2; $OCHF_2$; CF_3; OCF_3; and such moieties may also be optionally substituted by a fused-ring structure or bridge, for example -OCH_2O-.

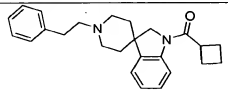
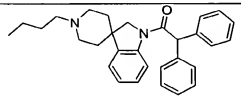
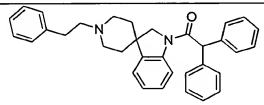
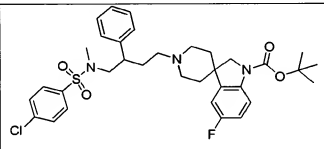
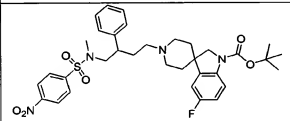
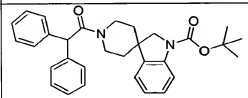
These substituents may optionally be further substituted with a substituent selected from such groups.

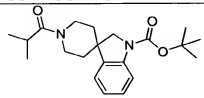
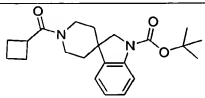
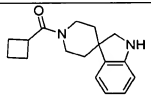
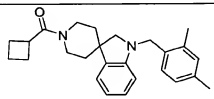
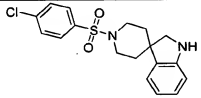
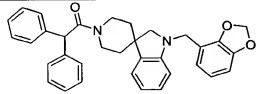
4.6 Illustrative Compounds of the Invention

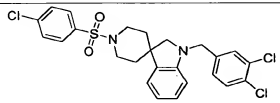
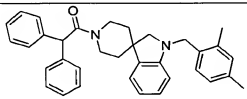
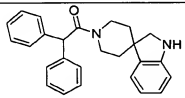
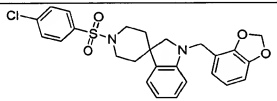
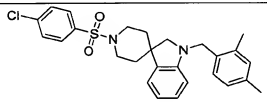
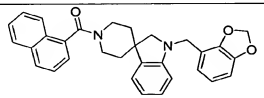
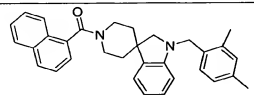
Set forth below are illustrative Compounds of the Invention including their retention time (RT) and mass to charge ration (m/z) by high-performance liquid chromatography-mass spectrometry (HPLC/MS) analysis.

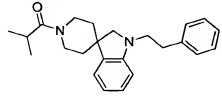
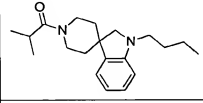
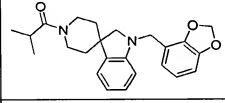
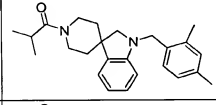
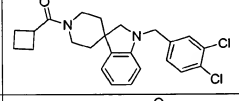
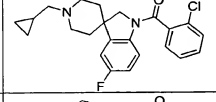
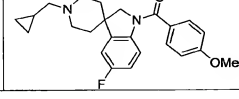
Table 1

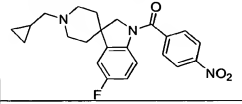
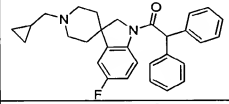
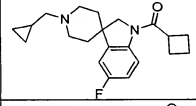
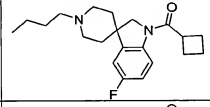
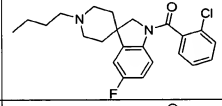
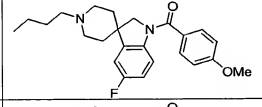
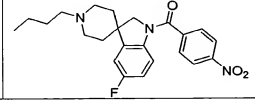
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
1		A	3.08	327.5
2		A	3.42	439.4
3		A	3.37	375.2
4		A	3.57	487.2
5		A	2.03	327.3

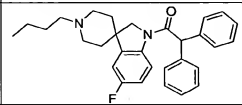
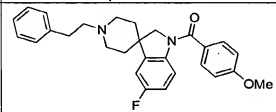
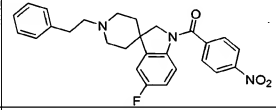
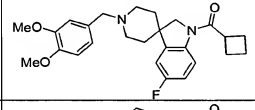
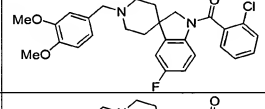
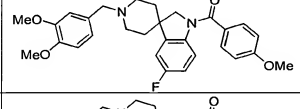
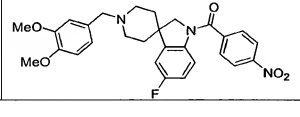
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
6		A	2.29	375.2
7		A	2.63	439.5
8		A	2.81	487.4
9		C	2.83	642.4
10		C	2.73	653.5
11		A	3.53	483.2

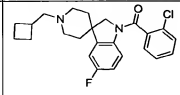
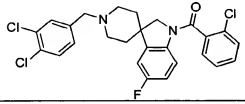
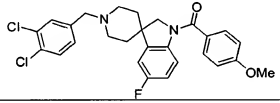
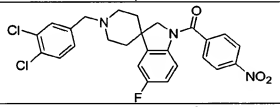
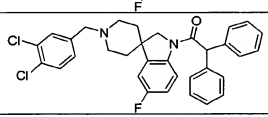
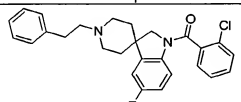
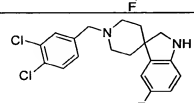
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
12		A	3.02	359.1
13		A	3.15	371.1
14		A	1.44	271.1
15		B	3.63	389.5
16		A	2.03	363.3
17		A	3.45	517.4

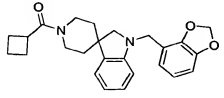
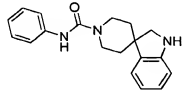
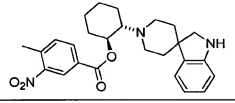
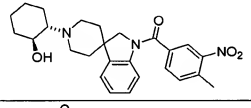
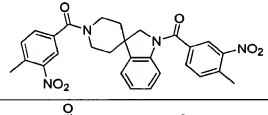
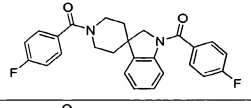
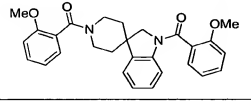
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
18		A	3.8	521.1
19		B	3.79	501.5
20		A	2.13	383.3
21		B	3.43	497.2
22		B	3.77	481.4
23		B	3.4	477.4
24		B	3.79	461.1

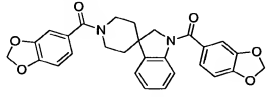
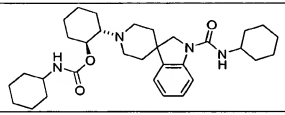
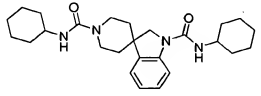
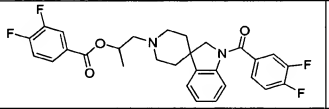
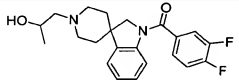
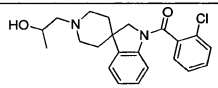
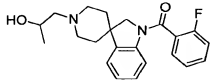
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
25		A	3.25	363.3
26		B	2.91	315.3
27		B	3.08	393.2
28		B	3.53	377.4
29		A	3.7	429.3
30		C	1.83	399.2
31		C	1.81	395.3

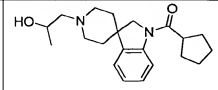
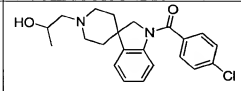
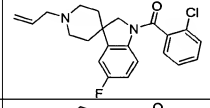
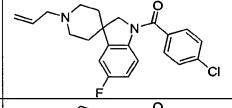
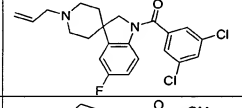
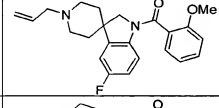
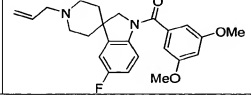
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
32		C	2.09	446.5
33		B	2.53	455.4
34		B	1.88	343.2
35		C	1.79	345.2
36		C	1.94	401.2
37		C	1.88	397.2
38		C	2.19	448.4

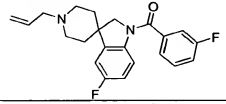
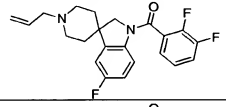
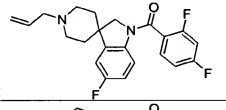
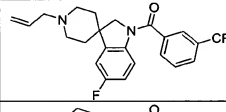
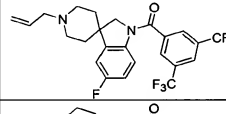
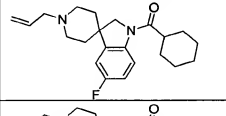
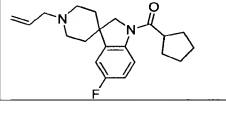
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
39		C	2.4	457.1
40		C	2.09	445.3
41		C	2.36	496.2
42		C	1.93	439.3
43		C	2.06	495.3
44		C	1.99	491.3
45		C	2.26	542.1

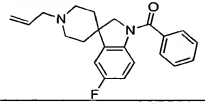
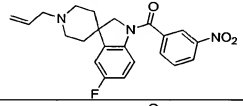
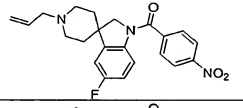
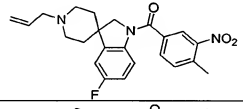
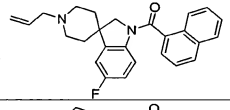
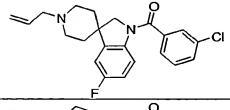
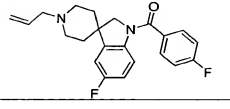
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
46		C	2.23	447.4
47		C	2.29	503.2
48		C	2.26	499.4
49		C	2.48	550.3
50		C	2.63	559.3
51		C	2.18	449.2
52		C	1.49	365.1

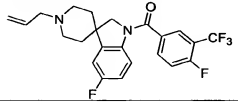
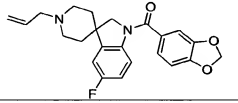
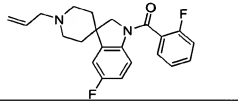
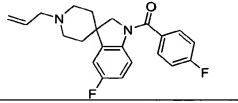
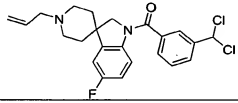
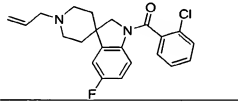
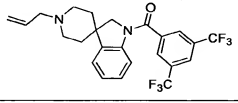
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
53		A	3.18	405.5
54		C	2.6	615.4
55		C	1.93	450.4
56		C	1.91	450.3
57		C	2.85	515.3
58		C	2.66	433.1
59		C	2.51	457.3

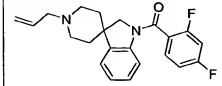
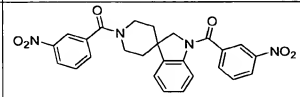
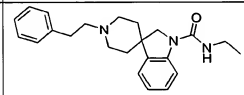
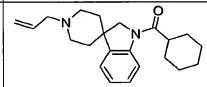
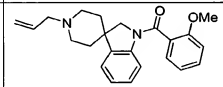
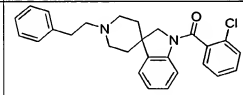
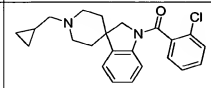
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
60		C	2.5	485.2
61		C	2.48	537.3
62		C	2.76	439.5
63		C	2.36	527.5
64		C	1.61	358.2
65		C	1.64	385.2
66		C	1.56	369.1

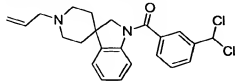
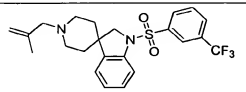
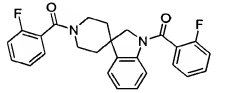
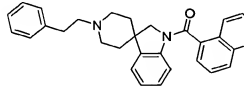
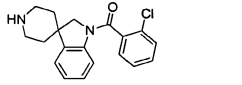
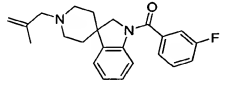
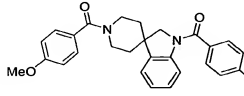
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
67		C	1.59	343.2
68		C	1.78	385.2
69		C	1.81	385.2
70		C	1.88	385.2
71		C	2.14	419.3
72		C	1.69	381.2
73		C	1.83	411.4

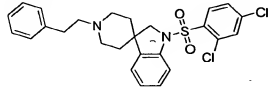
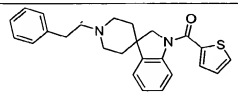
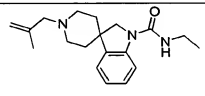
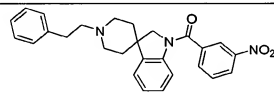
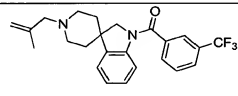
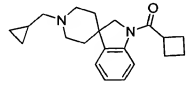
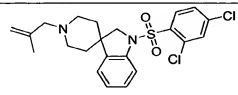
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
74		C	1.79	369.1
75		C	1.86	387.3
76		C	1.81	387.3
77		C	2.04	419.4
78		C	2.33	487.3
79		C	1.91	357.3
80		C	1.78	343.2

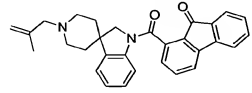
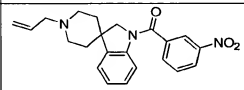
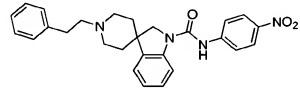
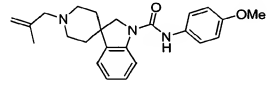
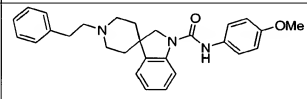
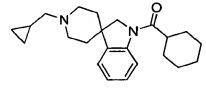
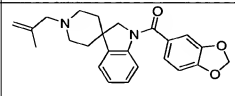
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
81		C	1.68	351.1
82		C	1.81	396.2
83		C	1.83	396.2
84		C	1.91	410.3
85		C	1.96	401.2
86		C	1.93	385.2
87		C	1.73	369.1

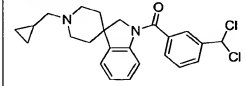
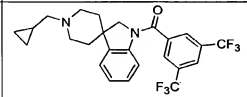
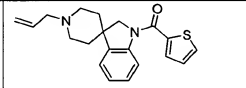
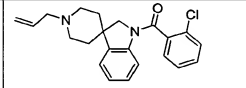
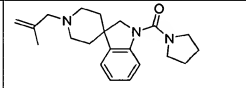
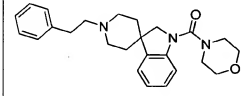
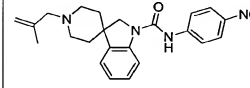
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
88		C	2.11	437.2
89		C	1.73	395.1
90		C	1.71	369.2
91		C	1.71	369.1
92		C	2.06	433.3
93		C	1.57	386.2
94		C	2.31	469.3

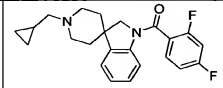
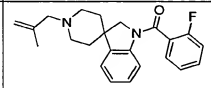
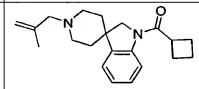
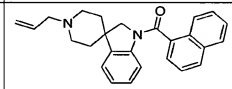
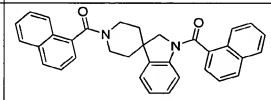
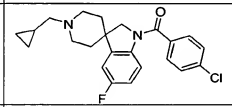
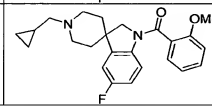
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
95		C	1.74	369.3
96		C	2.63	487.2
97		C	1.66	364.2
98		C	1.83	339.4
99		C	1.64	363.4
100		C	2.03	445.4
101		C	1.81	381.2

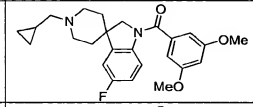
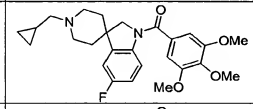
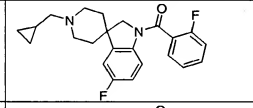
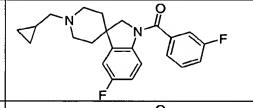
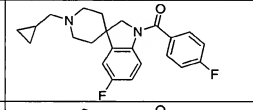
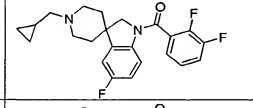
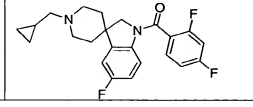
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
102		C	2.03	415.2
103		C	2.26	451.3
104		C	2.61	433.4
105		C	2.23	447.6
106		C	1.54	341.3
107		C	1.83	365.3
108		C	2.55	487.3

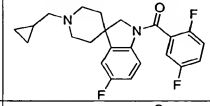
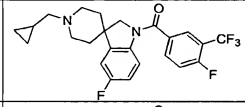
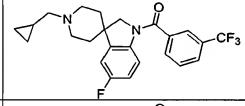
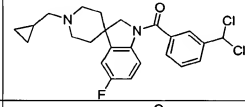
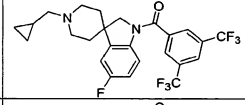
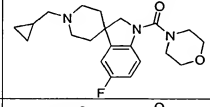
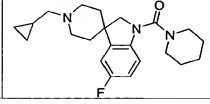
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
109		C	2.5	501.3
110		C	1.98	403.2
111		C	1.32	314.2
112		C	2.08	442.3
113		C	2.09	415.4
114		C	1.61	325.3
115		C	2.31	451.3

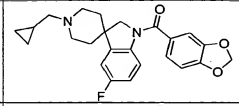
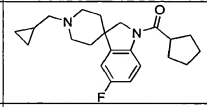
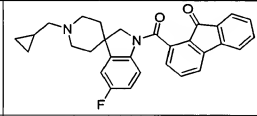
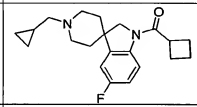
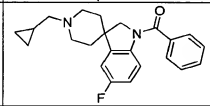
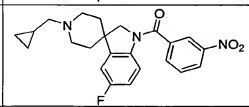
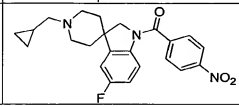
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
116		C	2.04	449.4
117		C	1.73	378.1
118		C	2.28	457.2
119		C	1.78	392.4
120		C	2.04	442.5
121		C	1.91	353.2
122		C	1.74	391.5

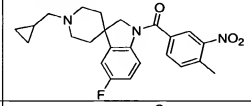
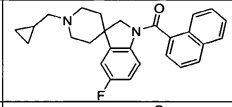
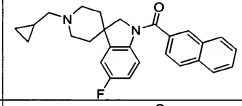
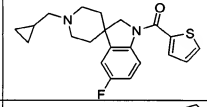
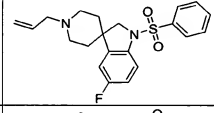
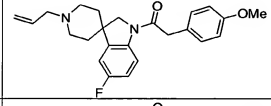
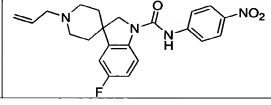
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
123		C	2.06	429.1
124		C	2.33	483.2
125		C	1.59	339.4
126		C	1.74	367.3
127		C	1.56	340.3
128		C	1.66	406.3
129		C	2.06	407.2

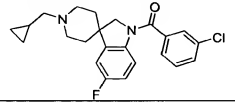
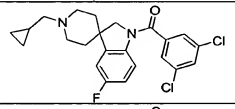
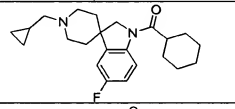
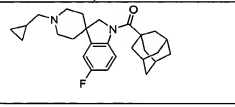
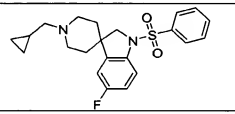
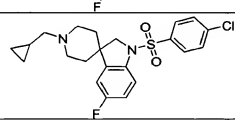
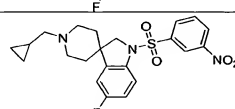
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
130		C	1.79	383.3
131		C	1.66	351.1
132		C	1.57	311.3
133		C	1.88	383.3
134		C	3.05	497.4
135		C	1.98	399.2
136		C	1.78	395.3

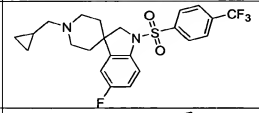
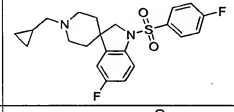
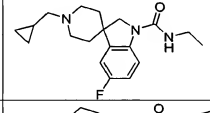
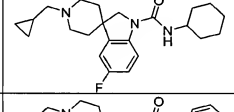
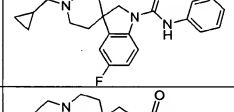
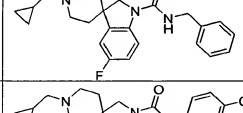
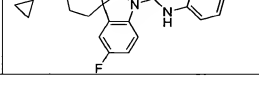
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
137		C	1.88	425.2
138		C	1.78	455.3
139		C	1.79	383.3
140		C	1.83	383.2
141		C	1.81	383.2
142		C	1.89	401.2
143		C	1.88	401.2

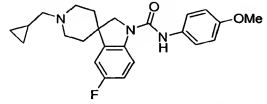
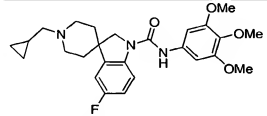
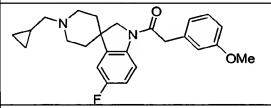
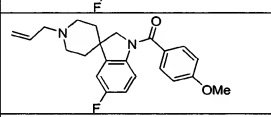
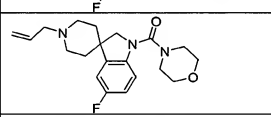
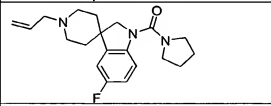
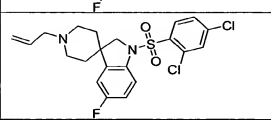
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
144		C	1.89	401.2
145		C	2.16	451.3
146		C	2.09	433.3
147		C	2.13	447.4
148		C	2.38	501.5
149		C	1.41	374.2
150		C	1.79	372.3

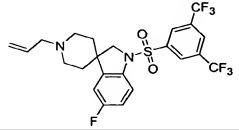
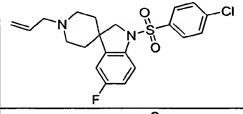
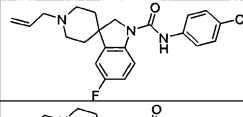
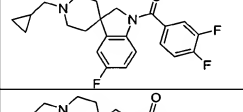
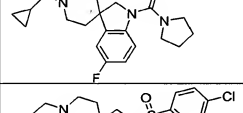
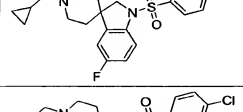
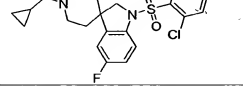
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
151		C	1.78	409.3
152		C	1.84	357.3
153		C	2.06	467.3
154		C	1.71	343.2
155		C	1.74	365.4
156		C	1.86	410.3
157		C	1.88	410.3

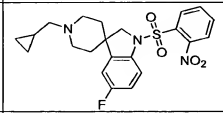
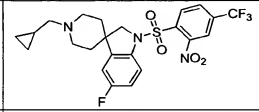
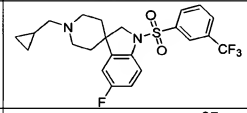
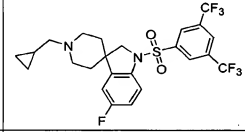
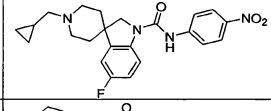
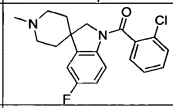
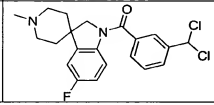
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
158		C	1.96	424.3
159		C	2.03	415.5
160		C	2.08	415.5
161		C	1.76	371.1
162		C	1.91	387.1
163		C	1.83	395.3
164		C	2.01	411.4

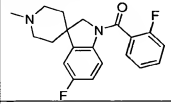
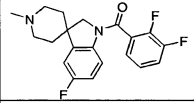
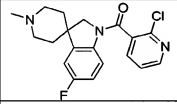
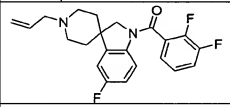
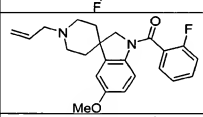
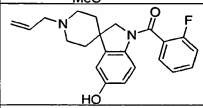
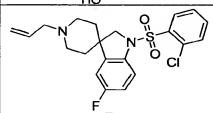
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
165		C	1.98	399.3
166		C	2.21	433.1
167		C	1.96	371.1
168		C	2.38	423.4
169		C	1.99	401.1
170		C	2.21	435.1
171		C	2.06	446.4

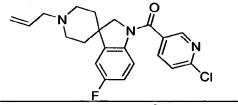
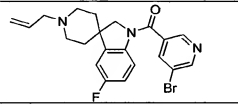
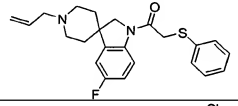
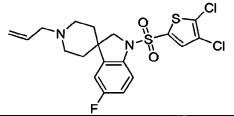
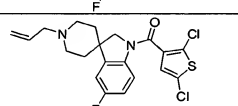
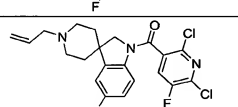
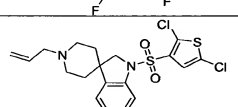
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
172		C	2.28	469.3
173		C	2.01	419.3
174		C	1.31	332.1
175		C	1.91	386.2
176		C	1.88	380.3
177		C	1.86	394.3
178		C	2.16	414.3

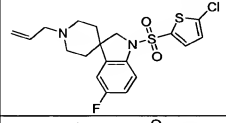
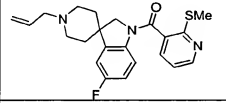
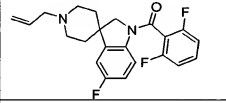
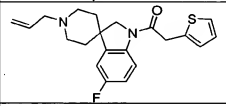
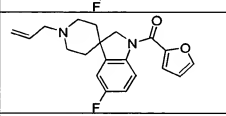
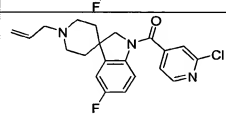
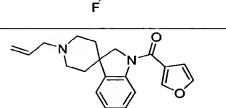
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
179		C	1.86	410.4
180		C	1.81	470.4
181		C	1.89	409.3
182		C	1.76	381.2
183		C	1.37	360.3
184		C	1.52	344
185		C	2.26	455.1

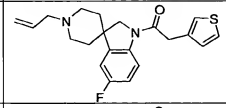
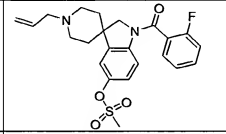
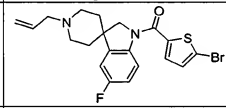
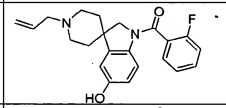
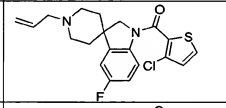
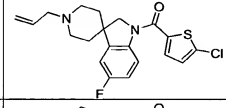
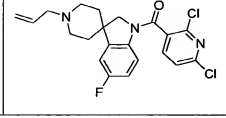
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
186		C	2.48	523.1
187		C	2.13	421.3
188		C	2.11	400.2
189		C	1.93	401.2
190		C	1.59	358.1
191		C	2.11	435.3
192		C	2.29	469.3

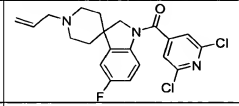
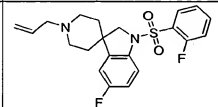
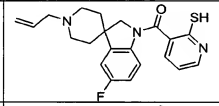
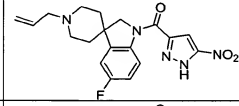
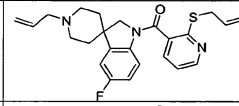
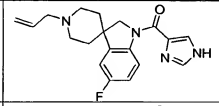
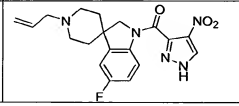
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
193		C	2.03	446.5
194		C	2.33	514.3
195		C	2.23	469.1
196		C	2.48	537.1
197		C	2.04	425.2
198		C	1.66	359.1
199		C	1.94	407.3

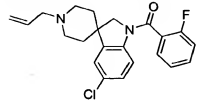
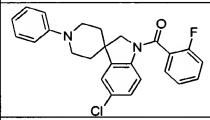
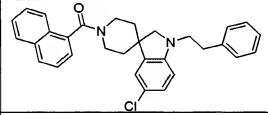
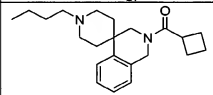
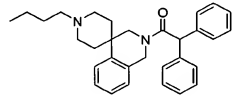
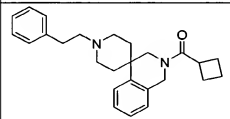
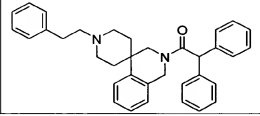
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
200		C	1.57	343.1
201		C	1.71	361.1
202		C	1.42	360.1
203		C	1.83	387.3
204		A	1.71	381.3
205		A	1.57	367.3
206		C	1.98	421.3

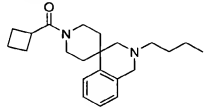
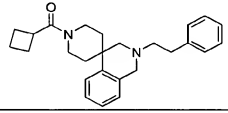
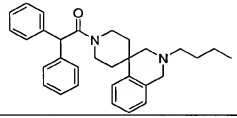
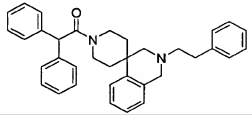
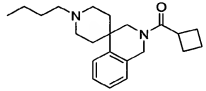
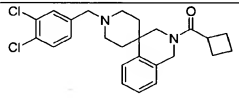
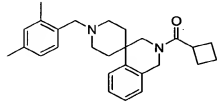
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
207		C	1.59	386.2
208		C	1.69	430.2
209		C	1.94	397.2
210		C	2.31	461.1
211		C	2.04	425.1
212		C	2.01	438.3
213		C	2.21	461

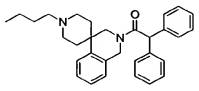
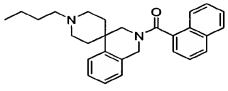
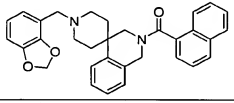
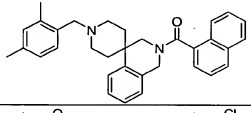
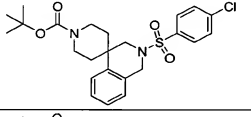
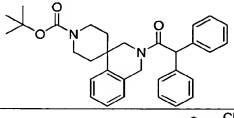
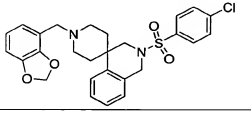
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
214		C	2.13	427.2
215		C	1.66	398.1
216		C	1.78	387.3
217		C	1.76	371.1
218		C	1.52	341.3
219		C	1.66	386.2
220		C	1.52	341.2

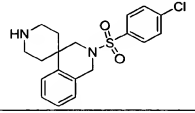
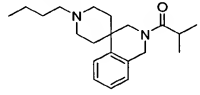
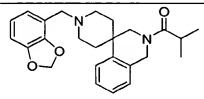
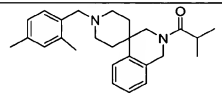
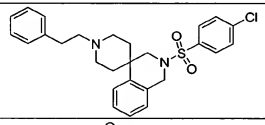
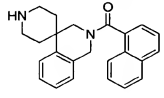
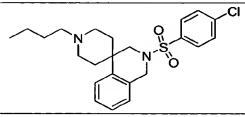
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
221		C	1.73	371.1
222		A	1.88	445.4
223				
224		A	1.57	367.3
225		C	1.79	391.2
226		C	2.03	391.2
227		C	1.84	420.3

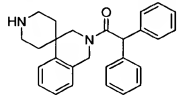
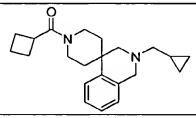
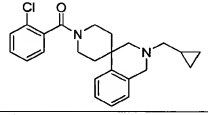
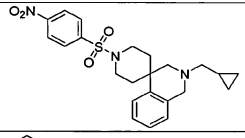
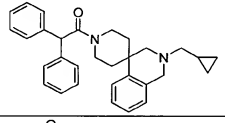
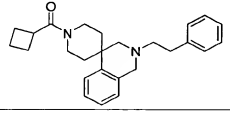
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
228		C	1.98	420.5
229		C	1.91	405.2
230		C	1.27	384.2
231		C	1.56	386.2
232		C	1.88	424.3
233		C	1.02	341.2
234		B	1.71	386.3

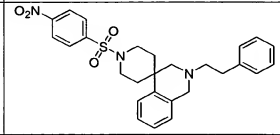
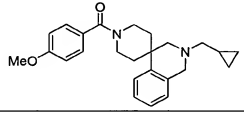
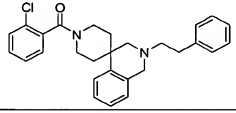
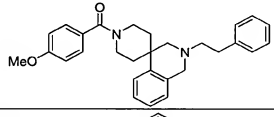
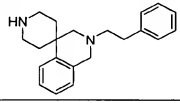
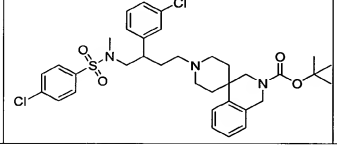
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
235		C	1.81	385.2
236		C	2.46	421.3
237		A	3.53	447.5
238		A	2.09	341.4
239		A	2.68	453.4
240		A	2.33	389.4
241		A	2.85	501.6

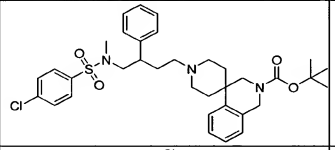
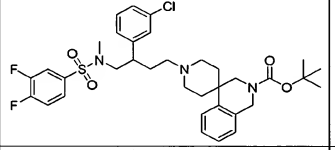
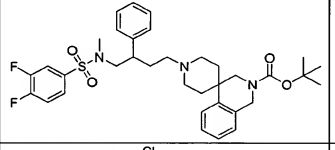
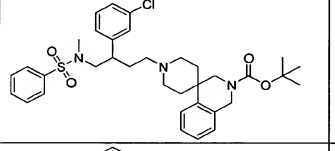
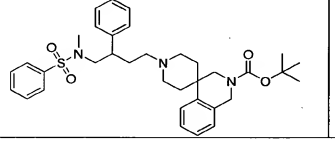
	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
242		A	1.89	341.3
243		A	2.16	389.3
244		A	2.55	453.4
245		A	2.7	501.6
246		C	1.74	341.4
247		C	2.18	443.3
248		C	2.11	403.4

	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
249		C	2.35	453.4
250		A	2.36	413.3
251		A	2.45	491.2
252		A	2.68	475.5
253		A	3.43	477.4
254		A	3.42	497.6
255		A	2.7	511.3

	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
256		A	2.18	377
257		B	1.91	329.2
258		B	2.13	407.1
259		B	2.36	391.3
260		B	2.7	481.2
261		A	2.01	357.2
262		B	2.56	433.4

	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
263		A	2.24	397.3
264		C	1.52	339.4
265		C	1.69	395.3
266		B	2.21	442.5
267		B	2.35	451.2
268		C	1.89	389.4

	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
269		C	2.29	492.4
270		C	1.64	391.3
271		C	2.03	445.4
272		C	1.98	441.2
273		C	1.17	307.4
274		B	3.12	672.2

	COMPOUND STRUCTURE	Mass Spec	RT (min)	m/z
275		B	2.98	638.3
276		B	3.03	674.5
277		B	2.91	640.5
278		B	2.96	638.3
279		B	2.85	604.5

The HPLC/MS data for the compounds of Table 1 were obtained as follows:

Method A:

HPLC/MS: Discovery® C18 column (5μ, 50 × 2.1 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 0.75 mL/min, ESI^+.

Method B:

HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, ESI^+.

Method C:

HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, ESI^+.

4.7 Definitions

As used herein, the terms used above have the following meaning:

"-(C_{1-8})alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 8 carbon atoms. Representative saturated straight chain -(C_{1-8})alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl and -n-octyl. Representative saturated branched -(C_{1-8})alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -2-methylbutyl, -3-methylbutyl, -2,2-dimethylbutyl, -2,3-dimethylbutyl, -2-methylpentyl, -3-methylpentyl, -4-methylpentyl, -2,2-dimethylhexyl, -3,3-dimethylhexyl, -1-ethylhexyl and the like.

"-(C_{1-6})alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative saturated straight chain -(C_{1-6})alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl. Representative saturated branched -(C_{1-6})alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -2-methylbutyl, -3-methylbutyl, -2,2-dimethylbutyl, -2,3-dimethylbutyl, -2-methylpentyl, -3-methylpentyl, -4-methylpentyl and the like.

"-(C_{1-4})alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 4 carbon atoms. Representative saturated straight chain

-(C_{1-4})alkyls include -methyl, -ethyl, -n-propyl, and -n-butyl. Representative saturated branched -(C_{1-4})alkyls include -isopropyl, -sec-butyl, -isobutyl, and -tert-butyl.

"-(C_{0-x})alkyl" means a direct bond or a saturated straight chain or branched non-cyclic hydrocarbon having up to X carbon atoms, such as those described above.

"-(C_{2-6})alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_{2-6})alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl and the like.

"-(C_{2-6})alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at lease one carbon-carbon triple bond. Representative straight chain and branched (C_{2-6})alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl and the like.

"Aryl" means a monocyclic, bicyclic or tricyclic carbocyclic, aromatic group containing from 6 to 14 carbon atoms in the ring. Representative examples include, but are not limited to, phenyl, tolyl, anthracenyl, phenanthryl, fluorenyl (*e.g.*, fluoren-9-one), indenyl, azulenyl, pyridinyl and naphthyl, as well as benzo-fused carbocyclic moieties including 5,6,7,8-tetrahydronaphthyl. An aryl group can be unsubstituted or substituted. In one embodiment, the aryl group is a phenyl group.

"-(C_{3-8}) cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C_{3-8})cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl and -cyclooctyl.

"-(C_{8-14}) bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_{8-14})bicycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

"-(C_{8-14}) tricycloalkyl" means a tri-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cycloalkyl ring. Representative -(C_{8-14})tricycloalkyls include -pyrenyl, -adamantyl, -1,2,3,4-tetrahydroanthracenyl,

-perhydroanthracenyl, -aceanthreneyl, -1,2,3,4-tetrahydropenanthrenyl, -5,6,7,8-tetrahydrophenanthrenyl, -perhydrophenanthrenyl and the like.

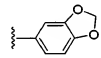
"-(C_5-$_{10}$) cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms. Representative (C_5-C_{10})cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl and the like.

"-(5 to 10 membered) heteroaryl" means an aromatic heterocycle ring of 5 to 10 members, including both mono- and bicyclic ring systems, where at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. In one embodiment one of the -(5 to 10 membered)heteroaryl's rings contain at least one carbon atom. In another embodiment both of the -(5 to 10 membered)heteroaryl's rings contain at least one carbon atom. Representative (5 to 10 membered)heteroaryls include pyridyl, furyl, benzofuranyl, benzo(1,3)dioxole, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl and the like.

"-(3 to 7 membered)heterocycle" or "-(3 to 7 membered)heterocyclo" means a 3- to 7-membered monocyclic heterocyclic ring which is either saturated, unsaturated, non-aromatic or aromatic. A 3- or a 4-membered heterocycle can contain up to 3 heteroatoms, a 5-membered heterocycle can contain up to 4 heteroatoms, a 6-membered heterocycle can contain up to 6 heteroatoms, and a 7-membered heterocycle can contain up to 7 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3 to 7 membered)heterocycle can be attached via any heteroatom or carbon atom. Representative -(3 to 7 membered)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl,

tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and the like.

"-(7 to 10 membered)bicycloheterocycle" or "-(7 to 10 membered) bicycloheterocyclo" means a 7 to 10 membered bicyclic, heterocyclic ring having a saturated, unsaturated, non-aromatic or aromatic group. A -(7 to 10 membered)bicycloheterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The (7 to 10 membered)bicycloheterocycle can be attached via any heteroatom or carbon atom. Representative -(7 to 10 membered)bicycloheterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, -benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, -β-carbolinyl, -benzo(1,3)dioxole and the like. A benzo(1,3)dioxole has the structure:



"Halogen" or "halo" mean -F, -Cl, -Br or -I.

"Hydroxy" or "hydroxyl" mean -OH.

"Amino" means $-NH_2$.

"Cyano" means -CN.

"Nitro" means $-NO_2$.

"Carboxy" means $-CO_2H$ or $-CO_2^-$.

The phrase "pharmaceutically acceptable salt," as used herein, is a salt formed from an acid and a basic nitrogen group of one of the Compounds of the Invention. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate))

salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a Compound of the Invention having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia and organic amines, such as unsubstituted or hydroxy-substituted mono-, di- or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl-N-ethylamine; diethylamine; triethylamine; mono-, bis- or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis- or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine and the like.

The terms, "polymorph(s)" and "polymorphic forms" and related terms herein refer to solid forms of the Compound of the Invention having different physical properties as a result of the order of the molecules in the crystal lattice. The differences in physical properties exhibited by solid forms affect pharmaceutical parameters such as storage stability, compressibility and density (important in formulation and product manufacturing), and dissolution rates (an important factor in determining bioavailability). Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolors more rapidly when comprised of one solid form than when comprised of another solid form) or mechanical changes (*e.g.*, tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable solid form) or both (*e.g.*, tablets of one solid form are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some solid form transitions may result in lack of potency or, at the other extreme, toxicity. In addition, the physical properties of the crystal may be important in processing, for example, one solid form might be more likely to form solvates or might be difficult to filter and wash free of impurities (*i.e.*, particle shape and size distribution might be different between one solid form relative to the other).

As used herein and unless otherwise indicated, the term "clathrate" means a Compound of the Invention, or a salt thereof, in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within.

As used herein and unless otherwise indicated, the term "hydrate" means a Compound of the Invention, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

As used herein and unless otherwise indicated, the term "prodrug" means a Compound of the Invention derivative that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound, particularly a Compound of the Invention. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a Compound of the Invention that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Preferably, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by *Burger's Medicinal Chemistry and Drug Discovery* 6th ed. (Donald J. Abraham *ed.*, 2001, Wiley) and *Design and Application of Prodrugs* (H. Bundgaard *ed.*, 1985, Harwood Academic Publishers Gmfh).

As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even

more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound.

The terms "isotopically" or "radio-labeled" refer to Compounds of the Invention which are identical to the Compounds of the Invention disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring) including, but not limited to, ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I.

A "patient" is defined herein to include any animal (*e.g.*, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig), in one embodiment a mammal such as a non-primate or a primate (*e.g.*, monkey or human), and in another embodiment a human. In certain embodiments, the human is an infant, child, adolescent or adult. In a particular embodiment, the patient is at risk for a cardiovascular or neurodegenerative disease or disorder. Patients who are at risk include, but are not limited to, those with hereditary history of cardiovascular or neurodegenerative diseases or disorders, or in a state of physical health which puts them at risk for a cardiovascular or neurodegenerative disease or disorder. In another embodiment, the patient has previously had a stroke or is at risk to have a stroke.

The phrase "effective amount" when used in connection with a Compound of the Invention means an amount effective for: (a) treating, preventing or managing a cardiovascular disease or disorder or a neurodegenerative disease or disorder; (b) preventing or reducing damage caused by a stroke; (c) inhibiting Mas receptor function in a cell capable of expressing Mas; or (d) detection by an instrument useful for detecting and/or measuring radioactivity (*e.g.*, a liquid scintillation counter).

The phrase "effective amount" when used in connection with another active agent means an amount for treating, preventing or managing a cardiovascular disease or disorder or a neurodegenerative disease or disorder while the Compound of the Invention is exerting its effect.

The phrases "treatment of," "treating" and the like include the amelioration or cessation of a cardiovascular disease or disorder or a neurodegenerative disease or disorder. In one embodiment, treating includes inhibiting, for example, decreasing the overall frequency of episodes of a cardiovascular disease or disorder or a neurodegenerative disease or disorder.

The phrases "prevention of," "preventing" and the like include the avoidance of the onset of a cardiovascular disease or disorder or a neurodegenerative disease or disorder. In one embodiment, neurological or cardiovascular damage caused by stroke is prevented.

The phrases "management of", "managing" and the like include the prevention of worsening of a cardiovascular disease or disorder or a neurodegenerative disease or disorder, or a symptom thereof.

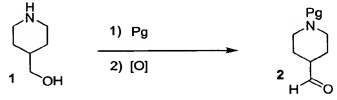
4.8 Methods for Making the Compounds of the Invention

The Compounds of the Invention can be made using conventional organic syntheses using known or commercially available starting materials and reagents and/or by the following illustrative methods.

The Compounds of the Invention can also be prepared according to methods set forth below.

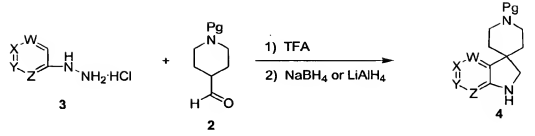
Scheme 1

Synthesis of spiroindoline/ spiroisoquinoline scaffold (Fischer-indole synthetic route)



4-piperidinemethanol (**Compound 1**) is protected with an appropriate protecting group (Pg) such as, but not limited to, Boc, Cbz, Alloc or Fmoc, followed by oxidation of the hydroxyl to give the above N-protected piperidinyl aldehyde (**Compound 2**).

Scheme 2

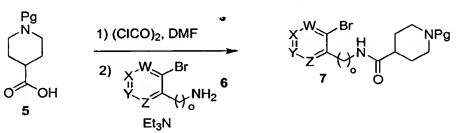


3 2 4

A component piece of the Compounds of the Invention can be prepared as shown above. A mixture of an appropriately substituted arylhydrazine (**Compound 3**) and a N-protected piperidine aldehyde (**Compound 2**) with an acid catalyst, such as trifluoroacetic acid, produces the indole. Reduction of the indole to the indoline (**Compound 4**) can be accomplished by a number of reducing agents including, but not limited to, lithium aluminum hydride and sodium borohydride. (*See, e.g.*, Maligres, P.E.; Houpis, I.; Rossen, K.; Molina, A.; Sager, J.; Upadhyay, V.; Wells, K. M.; Reamer, R.A.; Lynch, J.E.; Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron 53*:10983-10992 (1997)).

Scheme 3

Synthesis of spiroindoline/ spiroisoquinoline scaffold (via Palladium catalyzed intramolecular α-arylation)



5 6 7

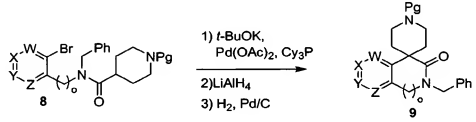
A component piece of the Compounds of the Invention can also be prepared by coupling of an amine (**Compound 6**) with an appropriately N-protected piperidine carboxylic acid (**Compound 5**) by mixing the amine and an activated carboxylate of the acid to give **Compound 7**. The piperidine amine can be protected with a variety of protecting groups (Pg) including, but not limited to, Boc, Cbz, Alloc or Fmoc. Activation of the carboxylate can be accomplished by conversion to the acid chloride

using oxalyl chloride and DMF or by *in situ* conversion to a reactive intermediate by treatment with a suitable coupling reagent (*e.g.*, EDC or BOP).

Scheme 4

The amide nitrogen of **Compound 7** can be masked with an appropriate protecting group that is orthogonal to other protective groups in the molecule to give **Compound 8**. For compounds where o = 0, benzyl is a suitable masking group.

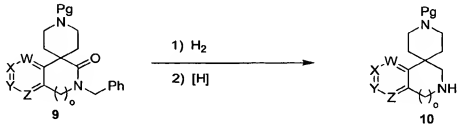
Scheme 5



The scaffold (**Compound 8**) is cyclized by treatment with a strong base, such as, but not limited to, potassium *tert*-butoxide, in the presence of a metal catalyst, such as, but not limited to, palladium acetate and a suitable ligand such as, but not limited to, tricyclohexylphosphine. Reduction of the carbonyl by a hydride reagent, such as, but not limited to, borane or lithium aluminum hydride, gives a differentially protected scaffold (**Compound 9**) which may be used to produce Compounds of the Invention.

Scheme 6

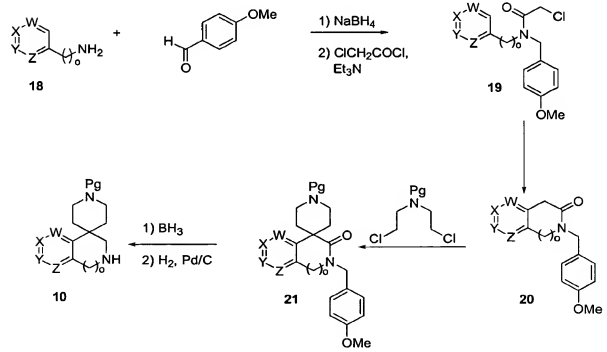
Conversion of spiroindoline/spiroisoquinoline to mono-protected- spiroindoline/ spiroisoquinoline (General procedure)



The amide group is then reduced to the amine and the benzylamino group is cleaved to give **Compound 10**.

Scheme 7

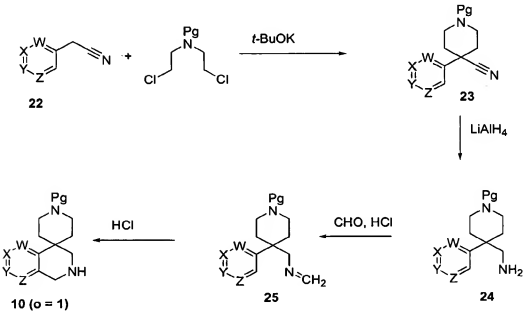
Synthesis of spiroindoline/ spiroisoquinoline scaffold



Alternatively, **Compound 10** can be prepared by reacting an aromatic amine (**Compound 18**) with *p*-methoxybenzaldehyde (as shown above) or benzaldehyde and a

reducing agent such as, but not limited to, sodium borohydride, to produce a benzyl protected analine. The protected amine is then coupled with chloroacetic acid via reaction with chloroacetyl chloride. The resulting amide (**Compound 19**) is cyclized via reaction with a suitable palladium catalyst to give the cyclic amide (**Compound 20**) (*See, e.g.*, Hennessey, E. J.; Buchwald, S. L. *J. Am. Chem. Soc. 125*: 12084-12085 (2003)). Double alkylation with a protected aminoalkyl halide produces the spirocyclic amide (**Compound 21**) which can be reduced to the amine by reagents such as, but not limited to, lithium aluminum hydride or borane to give **Compound 10**.

Scheme 8

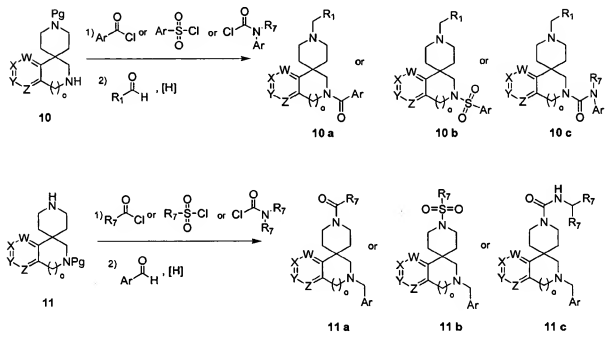


When o = 1, **Compound 10** can be synthesized by alkylation of a substituted or unsubstituted benzyl nitrile (**Compound 22**) by treatment with a strong base, such as, but not limited to, potassium *tert*-butoxide, and a protected bis(2-chloroethyl)amine to give the resulting nitrile (**Compound 23**). The nitrile can be reduced to the amine (**Compound 24**) with a reducing agent such as, but not limited to, lithium aluminum hydride, which is then reacted with formaldehyde to form the imine (**Compound 25**). An intramolecular Pictett-Spengler reaction, mediated by a strong acid, such as, but not

limited to, HCl, forms the monoprotected spirocyclic system (**Compound 10**, wherein o = 1) which can be used to produce the Compounds of the Invention.

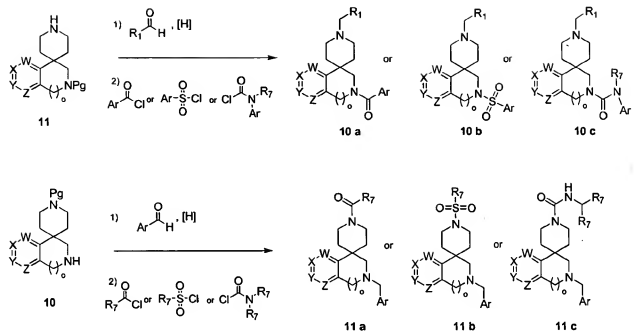
Scheme 9

General Methods for Parallel Synthesis-Functionalization of spiroindoline/spiroisoquinoline compounds



Synthesis of final products (**Compounds 10 a-c** and **11 a-c**) is generally accomplished in a library format using parallel synthesis techniques and can be performed on single compounds. The component pieces (**Compounds 10** and **11**) are acylated using acid chlorides or acids and a coupling reagent such as EDCI. The protecting group is removed using the appropriate conditions (*e.g.*, treatment with hydrochloric acid to remove a Boc group). The free amine can be alkylated by treatment with an alkyl halide or by reductive amination using an aldehyde and reducing agent such as sodium borohydride or sodium triacetoxyborohydride.

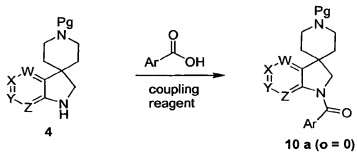
Scheme 10



Compounds 10 a-c and **11 a-c** can also be prepared from **Compounds 10** and **11** as shown above.

Scheme 11

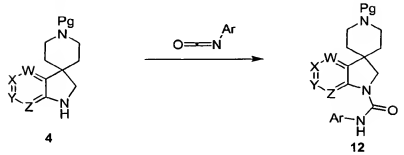
Alternative procedure for acylation of spiroindoline/spiroisoquinoline scaffolds (Direct coupling with carboxylic acid)



Compound 4 can be further reacted with an Ar-substituted carboxylic acid using a suitable coupling reagent such as, but not limited to, 1,3-diisopropylcarbodiimide (DIC), or reacted with and Ar-acid chloride to give **Compound 10 a** (wherein o = 0).

Scheme 12

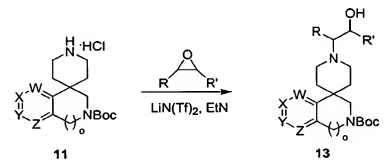
Synthesis of urea derivatives via reaction of spiroindolines/spiroisoquinolines with isocyanates



Compound 4 can be further reacted with an Ar-substituted isocynate to give **Compound 12.**

Scheme 13

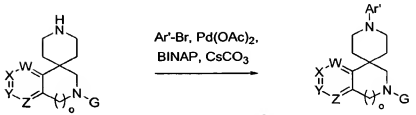
Ring-opening of epoxide with spiroindoline/spiroisoquinoline scaffolds



Compound 11 can be reacted with the above optionally substituted epoxide catalyzed by a Lewis acid such as, but not limited to, lithium triflamide to give **Compound 13. Compound 13** can be further reacted with various electrophiles as described above in Schemes 9 and 10.

Scheme 14

Aryl-substituted spiroindolines/spiroisoquinolines via Buchwald aminations of the piperidine ring

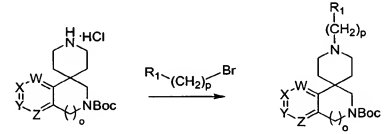


14 15

A deprotected amine (**Compound 14**) can be reacted with an aromatic halide in the presence of base and catalytic palladium/BINAP to give the N-aryl product (**Compound 15**).

Scheme 15

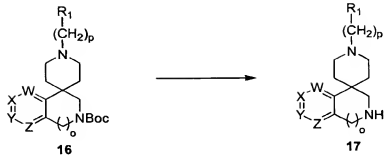
Functionalization of mono-Boc spiroindolines/spiroisoquinolines



11 16

Compound 11 can be functionalized at the pyridine nitrogen by reacting with an alkylating agent to give **Compound 16**.

Scheme 16



Compound 16 can then be deprotected to give **Compound 17**.

Synthetic methods for incorporating isotopes or radio-isotopes into organic compounds are applicable to the Compounds of the Invention and are well known in the art. Synthetic methods for incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas - This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [^{3}H] - This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

C. Reduction with Lithium Aluminum Hydride [^{3}H] - This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

D. Tritium Gas Exposure Labeling - This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. N-Methylation using Methyl Iodide [^{3}H] - This procedure is usually employed to prepare O-methyl or N-methyl [^{3}H] products by treating appropriate precursors with high specific activity methyl iodide [^{3}H]. This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include:

A. Sandmeyer and like reactions – This procedure transforms an aryl or heteroaryl amine into a diazonium salt, such as a tetrafluoroborate salt, and subsequently to ^{125}I labeled compound using Na^{125}I. A represented procedure is found in Zhu, D.-G. *et al.*, *J. Org. Chem. 67*, 943-948 (2002).

B. Ortho ^{125}Iodination of phenols – This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. *et al.*, *J. Labeled Compd Radiopharm. 42*, S264-S266 (1999).

C. Aryl and heteroaryl bromide exchange with ^{125}I – This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. $Pd(Ph_3P)_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., $(CH_3)_3SnSn(CH_3)_3$]. A represented procedure was reported by Bas, M.-D. *et al.*, *J. Labeled Compd Radiopharm. 44*, S280-S282 (2001).

Certain Compounds of the Invention can have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A Compound of the Invention can be in the form of an optical isomer or a diastereomer. Accordingly, the invention encompasses Compounds of the Invention and their uses as described herein in the form of their optical isomers, diasteriomers and mixtures thereof, including a racemic mixture. Optical isomers of the Compounds of the Invention can be obtained by known techniques such as chiral chromatography or formation of diastereomeric salts from an optically active acid or base.

In addition, one or more hydrogen, carbon or other atoms of a Compound of the Invention can be replaced by an isotope of the hydrogen, carbon or other atoms. Such compounds, which are encompassed by the present invention, are useful as research and diagnostic tools as well as in Mas receptor binding assays.

4.9 Therapeutic Uses of the Compounds of the Invention

In accordance with the invention, the Compounds of the Invention are useful as cardio-protective and/or neuro-protective agents. The Compounds of the Invention can also be administered to a patient in need of treatment, prevention and/or management of a cardiovascular or neurodegenerative disease or disorder.

In one embodiment, the cardiovascular disease or disorder is atherosclerosis, reperfusion injury, acute myocardial infarction, high blood pressure, primary or secondary hypertension, renal vascular hypertension, acute or chronic congestive heart failure, left ventricular hypertrophy, vascular hypertrophy, glaucoma, primary or secondary hyperaldosteronism, diabetic neuropathy, glomerulonephritis, scleroderma, glomerular sclerosis, renal failure, renal transplant therapy, diabetic retinopathy, or another vascular disorders such as migraine.

In another embodiment, the neurodegenerative disease or disorder is diabetic peripheral neuropathy, stroke, cerebral ischemia or Parkinson's disease.

In another embodiment, the Compounds of the Invention are useful as neuro-protective and/or cardio-protective agents and have the ability to prevent or lessen the severity of cerebral ischemia. In a certain embodiment, the cerebral ischemia results from stroke. Without being bound by any particular theory, it is thought that the Compounds of the Invention can prevent or lessen the severity of cerebral ischemia by preventing or lessening acute injury to ischemic neurons.

In another embodiment, the Compounds of the Invention are used in combination with, or in place of, angiotensin-converting enzyme (ACE) inhibitors to treat the diseases or disorders for which such ACE inhibitors are conventionally used. Such diseases or disorders include, but are not limited to, refractory hypertension, congestive heart failure, myocardial infarction, diabetes mellitus, chronic renal insufficiency, atherosclerotic cardiovascular disease, reinfarction, angina, end-stage renal disease, left ventricular dysfunction, or any disease or disorder associated with the renin-angiotensin system.

In one embodiment, an effective amount of a Compound of the Invention can be used to treat, prevent and/or manage any disease or disorder treatable, preventable and/or manageable by binding to the Mas receptor. Examples of diseases or disorders that are treatable or preventable by inhibiting binding to the Mas receptor include, but are not limited to, cardiovascular neurodegenerative diseases or disorders. In a particular embodiment, an effective amount of a Compound of the Invention can be used to treat, prevent and/or manage any disease or disorder treatable, preventable and/or manageable by inhibiting Mas receptor function.

Without wishing to be bound by theory, it is believed that the Compounds of the Invention act as inverse agonists for a Mas receptor. The term "inverse agonist" means a compound that binds to a receptor so as to reduce the baseline intracelluar response of the receptor observed in the absence of agonist.

The invention further relates to methods for inhibiting Mas function in a cell comprising contacting a cell capable of expressing Mas with an amount of a Compound of the Invention effective to inhibit Mas function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express Mas and, accordingly, is useful as part of an assay to select compounds useful for treating, preventing and/or managing a cardiovascular disease or disorder or a neurodegenerative disease or disorder. The method is also useful for inhibiting Mas function in a cell *in vivo*, such as in a patient, in a human in one embodiment, by contacting a cell, in a patient, with an amount of a Compound of the Invention effective to inhibit Mas function in the cell.

Preferred Compounds of the Invention for use in the methods described herein are those wherein G is -C(=O)-Ar. Still further preferred Compounds of the Invention for use in the methods described herein are those wherein G is -C(=O)-NH-Ar. Still further preferred Compounds of the Invention for use in the methods described herein are those wherein A and B are both $-(CH_2)_2-$. Still further preferred Compounds of the Invention for use in the methods described herein are those wherein Ar is substituted phenyl, preferable halogenated phenyl. Still further preferred Compounds of the Invention for use in the methods described herein are those wherein W, X, Y and Z are $-CR_3-$, $-CR_4-$, $-CR_5-$ and $-CR_6-$, respectively. Still further preferred Compounds of the Invention for use in the methods described herein are those wherein W, X and Y are -CH-, and Z is -CF-. Still further preferred Compounds of the Invention for use in the methods described herein are those wherein p is 1 and R_1 is cyclopropyl. Still further preferred Compounds of the Invention for use in the methods described herein are those wherein p is 1 and R_1 is $-CH=CH_2$.

4.10 Therapeutic/Prophylactic Administration and Compositions of the Invention

Due to their activity, the Compounds of the Invention are advantageously useful in veterinary and human medicine. As described above, the Compounds of the Invention

are useful for treating, preventing and/or managing a cardiovascular or neurodegenerative disease or disorder in a patient in need thereof. Accordingly, in one embodiment, the present invention relates to a method for manufacturing a medicament comprising one or more Compounds of the Invention and a pharmaceutically acceptable vehicle or excipient. In another embodiment, the medicament can further comprise another active agent.

When administered to a patient, the Compounds of the Invention can be administered as a component of a composition, such as a pharmaceutical composition, that comprises a pharmaceutically acceptable vehicle or excipient. The present compositions, which comprise a Compound of the Invention, can be administered intradermally, intramuscularly, intraperitoneally, intravenously, subcutaneously, intranasally, epidurally, orally, sublingually, intracerebrally, intravaginally, transdermally, rectally, by inhalation, topically (particularly to the ears, nose, eyes, or skin), by infusion or bolus injection, or by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, or intestinal mucosa) and can optionally be administered together with another active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules or capsules, and can be used to administer the Compound of the Invention.

In specific embodiments, it can be desirable to administer the Compounds of the Invention locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce the Compounds of the Invention into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the Compounds of the Invention can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the Compounds of the Invention can be delivered in a vesicle, in particular a liposome (*See* Langer, *Science* 249:1527-1533 (1990) and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989).

In yet another embodiment, the Compounds of the Invention can be delivered in a controlled-release system or sustained-release system (*See, e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*See Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the Compounds of the Invention, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The present pharmaceutical compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the patient.

The pharmaceutical compositions can be for a single, one-time use or can contain antimicrobial excipients, as described herein, rendering the pharmaceutical compositions suitable for multiple uses, for example a multi-use vial. In another embodiment, the

pharmaceutical compositions can be in unit dose or unit-of-use packages. As is known to those of skill in the art, a unit dose package provides delivery of a single dose of a drug to a subject. The methods of the invention provide for a unit dose package of a pharmaceutical composition comprising, for example, 700 mcg of a Compound of the Invention per unit. The 700 mcg of a Compound of the Invention, is an amount that administers 10 mcg/kg to a 70 kg subject, for example. The unit can be, for example, a single use vial, a pre-filled syringe, a single transdermal patch and the like.

As is known to those of skill in the art, a unit-of-use package is a convenient, prescription size, patient ready unit labeled for direct distribution by health care providers. A unit-of-use package contains a pharmaceutical composition in an amount necessary for a typical treatment interval and duration for a given indication. The methods of the invention provide for a unit-of-use package of a pharmaceutical composition comprising, for example, a Compound of the Invention in an effective amount for treating an average sized adult male or female. It will be apparent to those of skill in the art that the doses described herein are based on the subject's body weight.

The pharmaceutical compositions can be labeled and have accompanying labeling to identify the composition contained therein and other information useful to health care providers and subjects in the treatment of a cardiovascular or neurodegenerative disorder, including, but not limited to, instructions for use, dose, dosing interval, duration, indication, contraindications, warnings, precautions, handling and storage instructions and the like.

The term "label" refers to a display of written, printed or graphic matter upon the immediate container of an article, for example the written material displayed on a vial containing a pharmaceutically active agent.

The term "labeling" refers to all labels and other written, printed or graphic matter upon any article or any of its containers or wrappers or accompanying such article, for example, a package insert or instructional videotapes or DVDs accompanying or associated with a container of a pharmaceutically active agent.

Pharmaceutical excipients for use in the present pharmaceutical compositions can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The

pharmaceutical excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to an animal. Water, and in one embodiment physiological saline, is a particularly useful excipient when the Piperazine Compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsions, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (*See, e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Compounds of the Invention are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter

platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Compounds of the Invention can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lidocaine to lessen pain at the site of the injection. The ingredients can be supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the Compounds of the Invention are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the Compounds of the Invention are administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

The Compounds of the Invention can be administered by controlled-release or sustained-release means or by delivery devices that are known to those skilled in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions.

Suitable controlled- or sustained-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-sustained counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Compound of the Invention to treat or prevent a disease or disorder in a minimal amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Compound of the Invention, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Compound of the Invention that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Compound of the Invention to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Compound of the Invention in the body, the Compound of the Invention can be released from the dosage form at a rate that will replace the amount of the Compound of the Invention being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Compound of the Invention that is effective in the treatment or prevention of a disease or disorder can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the disorder and can be decided according to the

judgment of a practitioner and/or each patient's circumstances. Suitable effective dosage amounts, however, range from about 0.01 mg/kg of body weight to about 2500 mg/kg of body weight about every 4 h, although they are typically about 100 mg/kg of body weight or less. In one embodiment, the effective dosage amount ranges from about 0.01 milligrams to about 100 milligrams of a Compound of the Invention, in another embodiment, about 0.02 mg/kg of body weight to about 50 mg/kg of body weight, and in another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight. In one embodiment, an effective dosage amount is administered about every 12 h. In another embodiment, an effective dosage amount is administered about every 24 h. In another embodiment, an effective dosage amount is administered about every two days. In another embodiment, an effective dosage amount is administered twice a week. In another embodiment, an effective dosage amount is administered about once a week. In another embodiment, an effective dosage amount is administered about once every two weeks. In another embodiment, an effective dosage amount is administered about once per month.

Where a cell capable of expressing Mas is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting the Mas receptor function in a cell will typically range from about 0.01 μg/L to about 5 mg/L, in one embodiment, from about 0.01 μg/L to about 2.5 mg/L, in another embodiment, from about 0.01 μg/L to about 0.5 mg/L, and in another embodiment, from about 0.01 μg/L to about 0.25 mg/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention is from about 0.01 μL to about 1 mL. In another embodiment, the volume of solution or suspension is about 200 μL.

Where a cell capable of expressing Mas is contacted with a Compound of the Invention *in vivo*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 mg/kg of body weight to about 2500 mg/kg of body weight, although it typically ranges from about 100 mg/kg of body weight or less. In one embodiment, the effective dosage amount ranges from about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a Compound of the Invention, in another embodiment, about 0.02 mg/kg of body weight to about 50 mg/kg of body weight and in

another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight. In one embodiment, an effective dosage amount is administered about every 24 h. In another embodiment, an effective dosage amount is administered about every 12 h. In another embodiment, an effective dosage amount is administered about every 8 h. In another embodiment, an effective dosage amount is administered about every 6 h. In another embodiment, an effective dosage amount is administered about every 4 h.

The Compounds of the Invention can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in a humans. Animal model systems can be used to demonstrate safety and efficacy in humans.

The present methods for treating or preventing a disease or disorder in a patient in need thereof can further comprise administering another therapeutic agent to a patient being administered a Compound of the Invention. In one embodiment, the other therapeutic agent is administered in an effective amount.

The present methods for inhibiting Mas receptor function in a cell capable of expressing a Mas receptor can further comprise contacting the cell with an effective amount of another therapeutic agent.

Effective amounts of the other therapeutic agents are known to those skilled in the art. However, it is within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the invention, where another therapeutic agent is administered to an animal, the effective amount of the Compound of the Invention is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the Compounds of the Invention and the other therapeutic agent act synergistically to treat or prevent a cardiovascular or neurodegenerative disease or disorder.

The other therapeutic agents can be, but is not limited to, aspirin, nitrates (*e.g.* nitroglycerin), ACE inhibitors, beta-blockers, calcium channel blockers, statins, N-methyl-D-aspartate (NMDA) receptor antagonists, non-NMDA neuroprotective agents, free-radical scavengers, or any other agent useful for treating, preventing and/or managing a cardiovascular or neurodegenerative disorder or useful as a neuroprotective agent.

Examples of ACE inhibitors include, but are not limited to, trandolapril, benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril and ramipril.

Examples of beta-blockers include, but are not limited to, propranolol, verapamil, and divalproex.

Examples of calcium channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, and perhexiline.

Examples of NMDA receptor antagonists include, but are not limited to, selfotel, aptiganel and magnesium.

Examples of non-NMDA neuroprotective agents include, but are not limited to, nalmefene, lubeluzole and clomethiazole.

An example of a free-radical scavenger includes, but is not limited to, tirilizad.

Examples of useful therapeutic agents for treating or preventing Parkinson's disease include, but are not limited to, carbidopa/levodopa, pergolide, bromocriptine, ropinirole, pramipexole, entacapone, tolcapone, selegiline, amantadine, and trihexyphenidyl hydrochloride.

Examples of useful therapeutic agents for treating or preventing stroke include, but are not limited to, anticoagulants such as heparin, agents that break up clots such as streptokinase or tissue plasminogen activator, agents that reduce swelling such as mannitol or corticosteroids, and acetylsalicylic acid.

Examples of useful therapeutic agents for treating or preventing a migraine include, but are not limited to, sumatriptan, methysergide, ergotamine, caffeine and beta-blockers.

A Compound of the Invention and the other therapeutic agent(s) can act additively or, in one embodiment, synergistically. In one embodiment, a Compound of the Invention is administered concurrently with another therapeutic agent; for example, a composition comprising an effective amount of a Compound of the Invention, an effective amount of another therapeutic agent can be administered. Alternatively, a

composition comprising an effective amount of a Compound of the Invention and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a Compound of the Invention is administered prior or subsequent to administration of an effective amount of another therapeutic agent. In this embodiment, the Compound of the Invention is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Compound of the Invention exerts its preventative or therapeutic effect for treating or preventing a cardiovascular or neurodegenerative disorder.

In another embodiment, the Compound of the Invention is administered in combination with surgery associated with a cardiovascular or neurodegenerative disorder. Examples of surgery associated with a cardiovascular disorder include, but are not limited to, open-heart surgery, closed-heart surgery, coronary artery bypass surgery, heart valve surgery or angioplasty.

4.11 Diagnostic Uses of the Compounds of the Invention

The invention further relates to methods for assaying the ability of a Compound of the Invention to bind to a Mas receptor, comprising contacting a radio-labeled Compound of the Invention with a cell or tissue capable of expressing a Mas receptor.

Radio-labeled Compounds of the Invention including, but not limited to, those containing one or more ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I or ^{131}I atoms. The radionuclide that is incorporated in the radio-labeled Compound of the Invention will depend on the specific application of that radio-labeled compound. For example, for *in vitro* Mas receptor labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I, ^{131}I, or ^{35}S will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

Certain isotopically-labeled Compounds of the Invention are useful in compound and/or substrate tissue distribution assays. In certain embodiments, the Compounds of the Invention containing a ^{3}H and/or ^{14}C isotopes are useful in these studies. In other

embodiments, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability including, but not limited to, increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled Compounds of the Invention can generally be prepared by synthetic procedures analogous to those disclosed herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. It should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the more scarce radio-isotope or non-radioactive isotope.

In one embodiment, the invention relates to screening assays useful for identifying and/or evaluating Mas receptor binding ability of test compounds comprising the use of a radio-labeled Compound of the Invention. In general terms, a test compound can be evaluated for its ability to reduce binding of the radio-labeled Compound of the Invention to a Mas receptor. Accordingly, the ability of a test compound to compete with the radio-labeled Compound of the Invention for the binding to the Mas receptor directly correlates to its Mas receptor binding affinity.

In another embodiment, the invention relates to assays useful for locating or quantitating Mas receptor in a tissue sample, comprising contacting the tissue sample with an effective amount of a radio-labeled Compound of the Invention.

The radio-labeled Compounds of the Invention bind to the Mas receptor. In one embodiment the radio-labeled Compound of the Invention has an IC_{50} less than about 500 μM, in another embodiment the radio-labeled Compound of the Invention has an IC_{50} less than about 100 μM, in yet another embodiment the radio-labeled Compound of the Invention has an IC_{50} less than about 10 μM, in yet another embodiment the radio-labeled Compound of the Invention has an IC_{50} less than about 1 μM, in yet another embodiment the radio-labeled Compound of the Invention has an IC_{50} less than about 0.1 μM, in yet another embodiment the radio-labeled Compound of the Invention has an IC_{50} less than about 10 nM, and in still yet another embodiment the radio-labeled Compound of the Invention has an IC_{50} less than about 1 nM.

Other uses of the disclosed radio-labeled Compounds of the Invention and methods will become apparent to those in the art based upon, *inter alia*, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

4.12 Kits

The invention encompasses kits that can simplify the administration of a Compound of the Invention to an patient.

A typical kit of the invention comprises a unit dosage form of a Compound of the Invention. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Compound of the Invention and a pharmaceutically acceptable vehicle or excipient. The kit can further comprise a label or printed instructions instructing the use of the Compound of the Invention. The kit can also further comprise a unit dosage form of another therapeutic agent, for example, a second container containing an effective amount of the other therapeutic agent and a pharmaceutically acceptable vehicle or excipient. In another embodiment, the kit comprises a container containing an effective amount of a Compound of the Invention, an effective amount of another therapeutic agent and a pharmaceutically acceptable vehicle or excipient. Examples of other therapeutic agents include, but are not limited to, those listed above.

Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device include but are not limited to a syringe, a drip bag, a patch, an inhaler, and an enema bag.

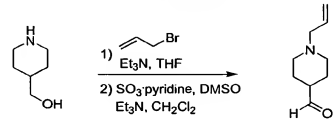
5. Examples

The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein.

5.1. Illustrative Compounds of the Invention

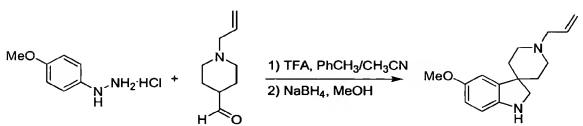
Examples 1-22 are illustrative Compounds of the Invention which were prepared using the methods set forth in Section 4.8 above.

5.1.1 Example 1



To a stirring solution of 4-piperidinemethanol (3.62 g, 31.4 mmol) and Et_3N (6.0 mL, 44.0 mmol) in THF (50 mL) was added allyl bromide (3.19 mL, 37.7 mmol). The reaction was stirred for about 5 h at ambient temperature, diluted with EtOAc (100 mL) and washed with H_2O (2 × 100 mL). NaOH (5N aq., 50 mL) was added to the aqueous phase followed by back-extraction of the aqueous phase with CH_2Cl_2 (2 × 100 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The resulting oil was dissolved in CH_2Cl_2 (83 mL) followed by the addition of Et_3N (6.8 mL, 50.13 mmol), DMSO (16 mL, 225 mmol), and SO_3.pyridine (5.32 g, 33.4 mmol). The mixture was stirred at room temperature for 15 h and washed with H_2O (2 × 100 mL). The aqueous phase was back extracted with CH_2Cl_2 (100 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated to give the resulting compound (2.08 g, 13.6 mmol, 43% overall yield) as a yellow oil.

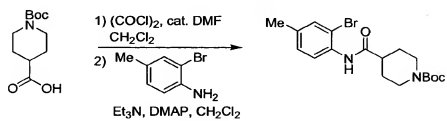
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.64 (1H, s), 5.85 (1H, m), 5.18 (1H, d, J = 16.8 Hz), 5.14 (1H, d, J = 8.4 Hz), 3.00 (2H, d, J = 6.4 Hz), 2.84 (2H, m), 2.24 (1H, m), 2.10 (2H, m), 1.90 (2H, m), 1.72 (2H, m).



To a flask under N_2 containing the above hydrazine (629 mg, 3.60 mmol) in degassed $PhCH_3/CH_3CN$ (50 : 1, v/v, 16 mL) and TFA (0.75 mL, 9.74 mmol), was added the above aldehyde (500 mg, 3.26 mmol) at room temperature. After stirring for 15 min at room temperature the reaction was heated to 37 °C and stirred for 20 h. The reaction was cooled to -5°C (ice/salt bath) and MeOH (20 mL) was added followed by the slow addition of $NaBH_4$ (185 mg, 4.89 mmol, added over 5 min). The reaction was stirred for 1 h, diluted with EtOAc (50 mL) and washed with NaOH (1M aq., 2 × 50 mL) and brine (50 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The material was purified by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ, 250 × 50 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 60 ml/min, λ = 214 nm. Products were isolated as mono-TFA salts after lyophilization. to give the resulting compound as the bis-TFA salt (740 mg, 1.52 mmol, 47% overall yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.72 (1H, d, J = 2.0 Hz), 6.60 (1H, d, J = 2.0 Hz), 6.59 (1H, s), 5.92 (1H, ddt, J = 16.8, 10.0, 6.4 Hz), 5.20 (1H, d, J = 17.2 Hz), 5.16 (1H, d, J = 10.4 Hz), 3.73 (3H, s), 3.42 (2H, s), 3.04 (2H, d, J = 6.4 Hz), 2.91 (2H, d, J = 12.0 Hz), 2.06 (2H, t, J = 13.6 Hz), 1.94 (2H, td, J = 13.2, 3.6 Hz), 1.75 (2H, d, J = 13.2 Hz). **HPLC/MS:** Discovery® C18 column (5μ, 50 × 2.1 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 0.75 mL/min, t_r = 0.92 min, ESI^+ = 259.2 (M + H).

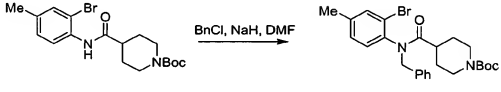
5.1.2 Example 2



To a solution of the *N*-Boc-piperidine-4-carboxylic acid (4.00 g, 17.5 mmol) in CH_2Cl_2 (80 mL) stirred under N_2 at room temperature was added oxalyl chloride (1.50 mL, 17.2 mmol) followed by DMF (68 uL, 0.88 mmol). The reaction was stirred for 1 h and Et_3N (5.5 mL, 40 mmol) was added followed by the addition of 2-bromo-4-methyl

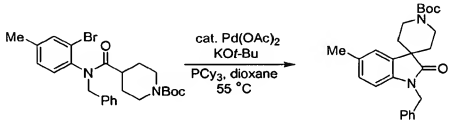
aniline (2.60 mL, 20.8 mmol) and 4-(dimethylamino) pyridine (210 mg, 1.72 mmol). After stirring for 18 h at room temperature , the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed sequentially with HCl (1N aq.,3 × 100 mL) and $NaHCO_3$ (sat. aq., 100 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (15% ethyl acetate in hexanes) gave 4-(2-Bromo-4-methyl-phenylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester (2.75 g, 6.94 mmol, 40% yield) as a white powder.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.20 (1H, d, J = 8.3 Hz), 7.63 (1H, s), 7.37 (1H, bs), 7.13 (1H , dd, J = 8.4, 1.4 Hz) 4.20 (2H, d, J = 12.9 Hz) 2.85 (2H, t, J = 11.9 Hz) 2.45 (1H, tt, J = 11.5, 3.8 Hz) 2.3 (3H, s), 1.95 (2H, d, J = 11.4 Hz) 1.82-1.7 (2H, dq, J = 12.0, 4.3 Hz) 1.48 (9H, s). **HPLC/MS:** C18 (0.0 × 0.0 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, X mL/min, t_r = x.xx min, ESI+ = 346.X (M + H).



To a solution of NaH (118 mg, 4.91 mmol) in anhydrous DMF (1.9 mL) at 0 °C was added 4-(2-Bromo-4-methyl-phenylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester (1.50 g, 3.79 mmol) as a solution in anhydrous DMF (2.3 mL added drop-wise). The resulting solution was stirred for 30 min while warming to room temperature . The reaction was cooled to 0 °C and benzyl chloride (0.45 mL, 3.78 mmol) was added. The reaction was warmed slowly to room temperature and stirred under N_2 for 18 h. The reaction was quenched by the addition of NH_4Cl (sat. aq., 20 mL) and the mixture was extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (30 mL) and dried over MgSO4. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to give 4-[Benzyl-(2-bromo-4-methyl-phenyl)-carbamoyl]-piperidine-1-carboxylic acid tert-butyl ester (1.65g, 3.39 mmol, 89% yield) as a white powder.

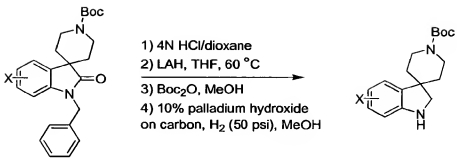
^{1}**H NMR** (400MHz, $CDCl_3$): δ 7.51 (1H, d, J = 1.2 Hz), 7.25 (3H, m), 7.16 (2H, m), 6.95 (1H, dd, J = 8.0, 1.3 Hz), 6.61 (1H, d, J = 8.0 Hz), 4.07 (1H, d, J = 13.2 Hz), 4.00 (1H, d, J = 13.2 Hz), 3.94 (1H, d, J = 14.4 Hz), 2.45 (1H, td, J = 12.9, 2.8 Hz), 2.35-2.25 (4H, m), 2.12 (1H, tt, J = 11.3, 3.7 Hz), 1.80 (1H, m), 1.68-1.55 (2H, m), 1.45 (1H, m), 1.37 (9H, s). **HPLC/MS:** C18 (0.0 × 0.0 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, X mL/min, ESI+ = 346.X (M + H).



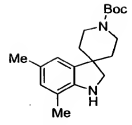
To a 250 mL Schlenck flask (w/injection port) containing $Pd(OAc)_2$ (54 mg, 0.24 mmol) was added PCy_3 (68 mg,, 0.24 mmol) as a solution in dioxane (420 μL). To the same flask was then added KO*t*Bu as a 1M solution in THF (4.24 mL, 4.24 mmol). 4-[Benzyl-(2-bromo-4-methyl-phenyl)-carbamoyl]-piperidine-1-carboxylic acid tert-butyl ester (1.18g, 2.42 mmol) in dioxane (17 mL) was then added and the resulting solution was stirred under nitrogen, at 55 °C for 18 h. After cooling to room temperature the reaction was diluted with ethyl acetate (75 mL) and washed with NH_4Cl (sat. aq., 3 × 70 mL and brine (70 mL). The organic layer was dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (5% ethyl acetate in hexanes) gave the resulting spiroindoline (981 mg, 2.41 mmol, 99% yield).

^{1}**H NMR** (400MHz, C*D*Cl_3): δ 7.33-7.24 (5H, m), 7.11 (1H, s), 6.97 (1H, d, J = 7.9 Hz), 6.54 (1H, d, J = 7.9 Hz), 4.85 (2H, s), 3.90-3.83 (4H, m), 2.31 (3H, s), 1.88-1.65 (4H, m), 1.50 (9H, s). **HPLC/MS:** Discovery® C18 column (5μ, 50 × 2.1 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 0.75 mL/min, t_r = 3.42 min, ESI^+ = 407.4 (M + H).

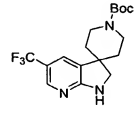
5.1.3 Example 3



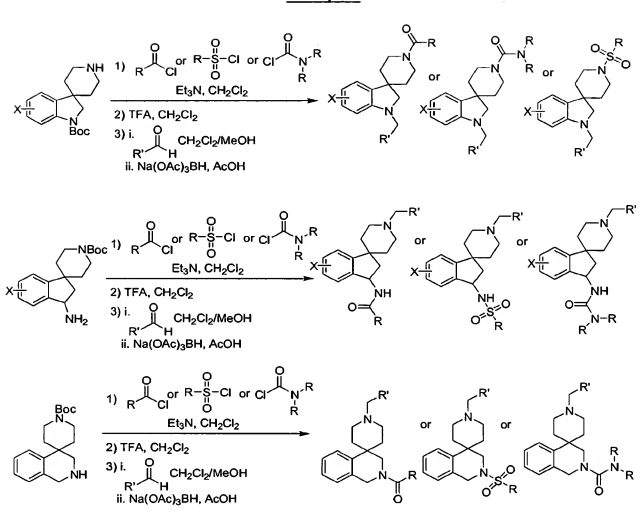
The above spiroindoline (prepared similarly as described in Example 2, above) (1.52 mmol, 1.0 equiv.) was treated with 4N HCl/dioxane (11 mL) for 2 h at room temperature . The volatiles were removed *in vacuo* and the residue was dissolved in EtOAc (25 mL) and washed with NaOH (1M aq., 25 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The concentrate was dissolved in THF (1.4 mL) and cooled to 0°C. A solution of LAH (1M in THF, 4 mL, 2.6 equiv.) was added and the mixture was warmed slowly to room temperature . A reflux condenser was attached and the reaction was heated to 60°C under N_2 for 16 h. The reaction was monitored by LC/MS and, if necessary, additional LAH was added until the reaction was complete. After cooling to room temperature the reaction was quenched by the addition of H_2O (0.5 mL). The mixture was diluted with EtOAc (25 mL), washed sequentially with NaOH (1M aq., 25 mL) and brine (25 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The concentrate was dissolved in MeOH (4 mL) and treated with Boc_2O (1.3 equiv. based on mass of mono-benzylated product). The reaction was stirred for 20 h at room temperature, diluted with EtOAc (25 mL), and washed with NaOH (1M aq., 25 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The crude mono-Boc/benzyl-spiroindole was added to a 27 mL reaction vessel containing 10% palladium hydroxide on carbon (32 mg) and methanol (20 mL). The solution was placed under H_2 atmosphere at 50 psi, and shaken for 18 h. The solution was filtered and concentrated *in vacuo*. Purification by silica gel chromatography (5% methanol in CH_2Cl_2) gave compound the mono-Boc spiroindole products. Exemplary compounds prepared using this methodology are shown below:



^{1}**H NMR** (400MHz, C*D*Cl$_3$): δ 6.75 (s, 1H) 6.68 (s, 1H) 4.15-3.95 (d, J=13.4, 2H) 3.4 (s, 2H) 3.0-2.85 (m, 2H) 2.2 (s, 3H) 2.05 (s, 3H) 1.75-1.65 (m, 2H) 1.65-1.55 (m, 2H) 1.48 (s, 9H).



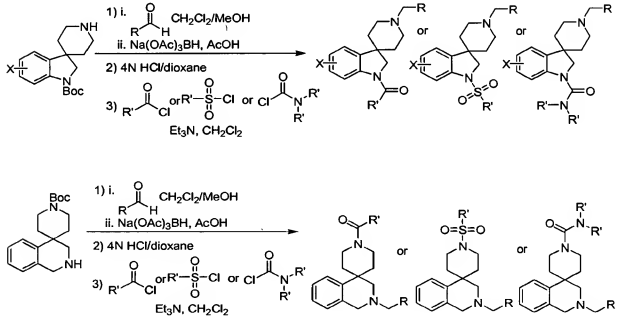
5.1.4 Example 4



To a solution Boc-spirocycle (Boc-spirocycles are commercially available from WuXi PharmaTech Co., Ltd., Shanghai 200131, China) (2.0 mmol, 1.0 equiv.) and Et_3N (3.0 mmol, 1.5 equiv.) in CH_2Cl_2 (3.5 mL) at room temperature was added acid/carbamoyl/ sulfphonyl chloride (2.0 mmol, 1.0 equiv.) as a solution in CH_2Cl_2 (4 mL). Reactions were stirred for 4 h and washed with HCl (1M aq., 5 mL) and $NaHCO_3$ (sat. aq., 5 mL). Organics were dried over Na_2SO_4, filtered, and concentrated. To the concentrate was added 20% TFA/DCM (v/v, 6 mL) and the reaction was stirred for 20 h at ambient temperature at which time NaOH (2.5 N aq., 10 mL) was added. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated.

The reductive aminations were performed on split portions of the deprotected products as described: To the amine (~0.4 mmol, 1.0 equiv.) in CH_2Cl_2/MeOH (4:1, v/v, 5 mL) was added aldehyde (0.4 mmol, 1.0 equiv.) at room temperature. The reaction was stirred for 5 h at room temperature at which time AcOH (0.8 mmol, 2.0 equiv.) and $Na(OAc)_3BH$ (0.8 mmol, 2.0 equiv.) were added. The reactions were stirred for an additional 20 h, diluted with CH_2Cl_2 (5 mL), and washed with NaOH (1M aq., 8 mL). The reactions were concentrated and purified by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ, 250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 ml/min, $\lambda = 214$ nm. Products were isolated as mono-TFA salts after lyophilization.

5.1.5 Example 5

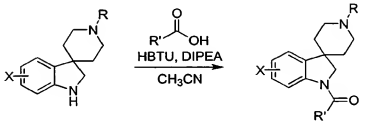


To a solution of Boc-spirocycle (0.86 mmol, 1.0 equiv.) in DCM/MeOH (4 : 1, v/v, 3.5 mL) was added aldehyde (1.7 mmol, 2.0 equiv.) at room temperature . After stirring for 5 h, AcOH (2.58 mmol, 3.0 equiv.) and $Na(OAc)_3BH$ (1.72 mmol, 2.0 equiv.) were added. Reactions were stirred for 20 h, diluted with CH_2Cl_2 (5 mL) and washed with NaOH (1M aq., 6 mL). The organics were dried over Na_2SO_4, filtered, and

concentrated. The Boc-group was removed by stirring in 4N HCl/dioxane for 4 h at room temperature followed by removal of volatiles *in vacuo*.

The acylation/sulphonylation/carbamoylations were performed on split portions of the deprotected spirocycles as described herein. To the amine (~0.11 mmol, 1.0 equiv.) in DCM (5 mL) containing Et_3N (0.37 mmol) at room temperature was added acid/sulphonyl/carbamoyl chloride (0.22 mmol, 2.0 equiv.). After stirring for 48 h at ambient temperature the reactions were washed with $NaHCO_3$ (sat. aq., 5 mL) and H_20 (2 × 5 mL). The organics were dried over Na_2SO_4 and loaded on Silacycle® 12mL-2g Si-Tosic Acid SPE cartridges. MeOH (10 mL) was passed through the column to remove unbound impurities. The product was then eluted by passing a solution of 2N NH_3 in MeOH (10 mL) through the column. The fractions were concentrated and, if necessary, purified by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ, 250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 ml/min, $\lambda = 214$ nm. Products were isolated as mono-TFA salts after lyophilization.

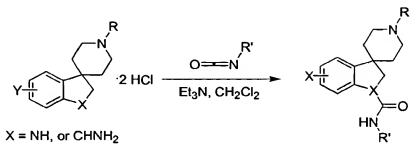
5.1.6 Example 6



To a solution of a spiroindoline (0.124 mmol, 1.0 equiv.) in CH_3CN (1.5 mL) at room temperature was added sequentially DIPEA (0.248 mmol, 2.0 equiv.), carboxylic acid (0.173 mmol, 1.4 equiv.), and HBTU (0.173 mmol, 1.4 equiv.). Reactions were stirred for 48 h at room temperature and diluted with CH_2Cl_2 (5 mL) and washed sequentially with $NaHCO_3$ (sat. aq., 5 mL), HCl (1M aq., 5 mL), and water (5 mL). Organics were dried over Na_2SO_4, filtered, and concentrated. Products were purified by 'trap and release' on Silacycle® 12mL-2g Si-Tosic Acid SPE cartridges as described previously (see: parallel synthesis of spiroindole/spiropiperidines). If necessary, samples were further purified by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ,

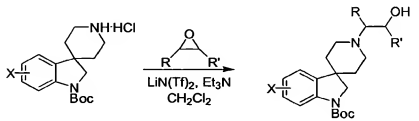
250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 ml/min, $\lambda = 214$ nm.

5.1.7 Example 7



To a stirring solution of a spirocycle (0.11 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) containing Et_3N (0.37 mmol, 3.4 equiv.) at room temperature was added isocyanate (0.22 mmol, 2.0 equiv.). After stirring for 48 h the reactions were washed with $NaHCO_3$ (sat. aq., 4 mL) and H_20 (2 ×, 4 mL). The organics were dried over Na_2SO_4 and concentrated. Products were purified by 'trap and release' on Silacycle® 12 mL-2g Si-Tosic Acid SPE cartridges as described previously (see: parallel synthesis of spiroindole/spiropiperidines). If necessary, samples were further purified by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ, 250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 ml/min, $\lambda = 214$ nm.

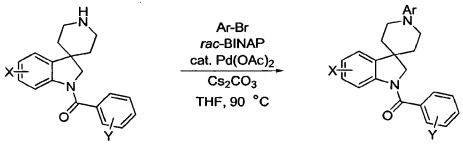
5.1.8 Example 8



A solution of the above amine (0.46 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at room temperature was treated sequentially with Et_3N (0.69 mmol, 1.5 equiv.), $LiN(Tf)_2$ (0.92 mmol, 2.0 equiv.), and epoxide (0.92 mmol, 2.0 equiv.). After stirring for 20 h the reactions were diluted with CH_2Cl_2 (5 mL), washed with $NaHCO_3$ (sat. aq., 2 × 5 mL),

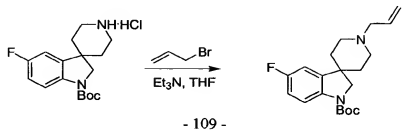
dried over Na_2SO_4, filtered, and concentrated. Material obtained was deprotected (as described previously) and reacted with various electrophiles (as described previously).

5.1.9 Example 9



To a 4 mL vial containing Cs_2CO_3 (0.17 mmol, 1.9 equiv.) was added a solution of $Pd(OAc)_2$ (4.5 μmol, 0.05 equiv.) and *rac*-BINAP (7.2 μmol, 0.08 equiv.) in anhydrous THF (1.0 mL). The aryl bromide (0.126 mmol, 1.40 equiv.) was added followed by the addition of piperidene/spiroindoline (0.09 mmol, 1.0 equiv.) as a solution anhydrous THF (2.0 mL). The vial was capped and heated with stirring to 90 °C for 4 to 8 hours (as monitored by HPLC/MS). The reaction mixture was transferred to a 40 mL vial and diluted with MTBE (8 mL). The organic layer was washed with HCl (1M aq., 2 × 3 mL) water (3 mL). The organic layer was concentrated and the residue was diluted with CH_2Cl_2 (8 mL) and dried over Na_2SO_4. Products were purified by 'trap and release' on Silacycle® 12mL-2g Si-Tosic Acid SPE cartridges as described previously (see: parallel synthesis of spiroindole/spiropiperidines). If necessary, sample was further purified by reverse-phase HPLC: Phenomenex® Luna C18 Column (10 μ, 250X21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% CH_3CN, 20 mL/min, λ = 214 nm.

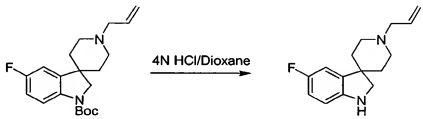
5.1.10 Example 10



To a stirring solution of the hydrochloride salt of the above spirocyle (1.50 g, 4.37 mmol) in THF (85 mL) at 0 °C was added Et_3N (1.52 mL, 10.9 mmol) and allyl bromide (0.69 g, 5.70 mmol). The reaction was slowly warmed to room temperature and stirred for 72 h. The mixture was filtered and concentrated. The concentrate was dissolved in EtOAc (50 mL), washed with H_2O (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to give the resulting compound (1.48 g, 4.32 mmol, 99% yield) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (3H, m), 5.88 (1H, ddt. J = 17.6, 9.6, 6.4 Hz), 5.20 (1H, d, J = 17.6 Hz), 5.17 (1H, d, J = 9.6 Hz), 3.75 (2H, m), 3.03 (2H, d, J = 6.4 Hz), 2.93 (2H, d, J = 11.6 Hz), 2.05 (2H, m), 1.90 (2H, td, J = 13.2, 3.6 Hz), 1.66 (2H, dd, J = 12.8, 1.6 Hz), 1.56 (9H, s). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.93 min, ESI^+ = 347.3 (M + H).

5.1.11 Example 11

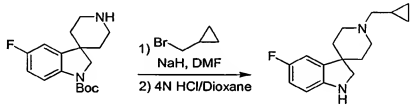


The above spiroindoline (797 mg, 2.33 mmol) was treated with 4N HCl in dioxane (5 mL) for 3 h at room temperature . The volatiles were removed *in vacuo* and the crude residue was washed with hexanes (2 × 10 mL) to give the bis-HCl salt of the resulting compound as a white solid. In order to prepare the free base of the resulting compound, the white solid was dissolved in CH_2Cl_2, washed with NaOH (1N aq.), dried over Na_2SO_4, filtered, and concentrated to give the resulting compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.78 (1H, dd, J = 8.4, 2.4 Hz), 6.72 (1H, td, J = 8.8, 2.8 Hz), 6.53 (1H, dd, J = 8.4, 4.4 Hz), 5.92 (1H, ddt, J = 18.0, 10.0, 6.4 Hz), 5.20 (1H, dd, J = 18.0, 1.6 Hz), 5.17 (1H, dd, J = 10.0, 0.8 Hz), 3.44 (2H, s), 3.03 (2H, d, J =

6.4 Hz), 2.90 (2H, dd, J = 9.2, 2.8 Hz), 2.06 (2H, td, J = 12.4, 2.4 Hz), 1.90 (2H, td, J = 13.2, 4.0 Hz), 1.75 (2H, dd, J = 13.2, 2.0 Hz), 1.73 (1H, bs). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 0.67 min, ESI^+ = 247.2 (M + H).

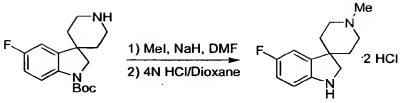
5.1.12 Example 12



To a flask containing NaH (30.0 mg, 1.25 mmol) in DMF (10 mL) under N_2 at room temperature was added compound the above spiroindoline compound (256 mg, 0.84 mmol) as a solution in DMF (3 mL). The flask was brought to 0 °C and (bromomethyl)-cyclopropane (121 μL, 1.25 mmol) was added via syringe. The reaction was slowly warmed to room temperature and stirred for 96 h under N_2. The reaction was quenched with NH_4Cl (sat. aq., 1 mL) and the mixture was diluted with EtOAc/hexanes (1 : 1, v/v, 25 mL) and washed with H_2O (2 × 25 mL). The organics were dried over MgSO4, filtered, and concentrated. The product was treated with 4N HCl/Dioxane (5 mL) and stirred for 4 h at room temperature followed by removal of the volatiles in vacuo to give the resulting compound as the bis-HCl salt. In order to prepare the resulting compound as the free base, the white solid was dissolved in CH_2Cl_2, washed with NaOH (1N aq.), dried over Na_2SO_4, filtered, and concentrated.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.78 (1H, m), 6.71 (1H, m), 6.53 (1H, m), 3.40 (2H, s), 3.02 (2H, m), 3.36 (2H, d, J = 9.6 Hz), 2.08 (2H, td, J = 12.0, 2.0 Hz), 1.93 (2H, td, J = 13.6, 4.0 Hz), 1.74 (2H, m), 0.89 (1H, m), 0.53 (2H, m), 0.11 (2H, m). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 0.74 min, ESI^+ = 261.1 (M + H).

5.1.13 Example 13



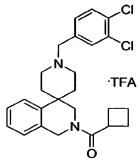
To a flask containing NaH (19.0 mg, 0.47 mmol) in DMF (2.5 mL) under N_2 at room temperature was added the above spiroindoline compound (96 mg, 0.31 mmol) as a solution in DMF (2.5 mL). The flask was brought to 0 °C and methyl iodide (29 μL, 0.47 mmol) was added via syringe. The reaction was stirred at 0 °C for 30 min at which time NH_4Cl (sat. aq., 1 mL) was added to quench remaining hydride. The mixture was diluted with EtOAc/hexanes (1 : 1, v/v, 15 mL) and washed with H_2O (4 × 10 mL). The product was treated with 4N HCl/dioxane (5 mL) for 5 h and concentrated *in vacuo* to give the bis-HCl salt of the resulting compound.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.40 (1H, bs), 7.12 (2H, m), 7.02 (1H, d, J = 8.0 Hz), 4.05-3.60 (2H, bs), 3.67 (2H, s), 3.43 (2H, d, J = 12.0 Hz), 3.10 (2H, q, J = 10.0 Hz), 2.77 (3H, d, J = 4.8 Hz), 2.17 (2H, td, J = 13.6, 3.6 Hz), 1.94 (2H, d, J = 14.0 Hz).

HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 0.70 min, ESI^+ = 221.0 (M + H).

Examples 14-22, below, were made using the methodology set forth herein.

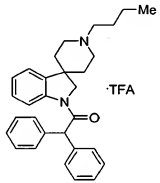
5.1.14 Example 14



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (1H, d, J = 2.0 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.54 (2H, m), 7.30 (1H, t, J = 7.6 Hz), 7.22 (1H, td, J = 7.6, 1.2 Hz), 7.05 (1H, d, J = 7.2 Hz),

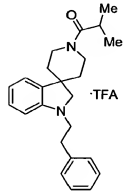
4.56 (2H, s), 4.16 (2H, s), 3.87 (2H, s), 3.48 (2H, d, J = 11.6 Hz), 3,37 (1H, q, J = 8.4 Hz), 3.11 (2H, t, J = 12.8 Hz), 2.57 (2H, td, J = 14.4, 2.0 Hz), 2.33-2.18 (4H, m), 2.03 (1H, m), 1.90 (1H, m) 1.80-1.60 (2H, m). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.18 min, ESI^+ = 443.3 (M + H).

5.1.15 Example 15



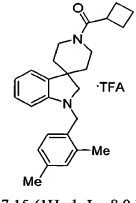
^{1}H NMR ($CDCl_3$, 400 MHz), A mixture of conformational isomers was evident: δ 8.30 (0.1H, d, J = 8.4 Hz), 8.18 (0.9H, d, J = 8.0 Hz), 7.33-7.16 (11H, m), 7.11-7.01 (2H, m), 5.14 (0.1H, s), 5.10 (0.9 H, s), 4.07 (0.2H, s), 3.84 (1.8H, s), 3.55 (0.2H, d, J = 8.0 Hz), 3.42 (1.8H, d, J = 12.0 Hz), 3.03-2.75 (2H, m), 2.42 (0.2H, m), 2.29 (1.8H, t, J = 13.6 Hz), 2.19 (2H, m), 1.90-1.56 (4H, m), 1.33 (2H, m), 0.91 (3H, t, J = 7.2 Hz). **HPLC/MS:** Discovery® C18 column (5μ, 50 × 2.1 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 0.75 mL/min, t_r = 2.63 min, ESI^+ = 439.5 (M + H).

5.1.16 Example 16



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (2H, m), 7.23 (3H, m), 7.13 (1H, td, J = 7.6, 1.2 Hz), 7.01 (1H, d, J = 6.8 Hz), 6.74 (1H, t, J = 7.2 Hz), 6.56 (1H, d, J = 7.6 Hz), 4.57 (1H, d, J = 13.2 Hz), 3.90 (1H, d, J = 12.0 Hz), 3.40 (3H, m), 3.29 (1H, m), 3.19 1H, m), 2.92 (2H, t, J = 7.6 Hz), 2.84 (1H, sept, J = 6.4 Hz), 2.7 (1H, m), 1.76 (4H, m), 1.16 (6H, m). **HPLC/MS:** Discovery® C18 column (5μ, 50 × 2.1 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 0.75 mL/min, t_r = 3.25 min, ESI^+ = 363.3 (M + H).

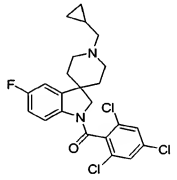
5.1.17 Example 17



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 (1H, d, J = 8.0 Hz), 7.10 (1H, td, J = 7.6, 1.2 Hz), 7.00 (3H, m), 6.70 (1H, td, J = 7.6, 1.0 Hz), 4.48 (1H, d, J = 13.6 Hz), 3.63 (1H, d, J = 13.2 Hz), 3.25 (1H, m), 3.19 (2H, m), 3.02 (1H, m), 2.72 (1H, m), 2.40 (2H, m), 2.33 (3H, s), 2.30 (3H, s), 2.13 (2H, m), 2.10-1.65 (8H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): 173.1, 151.4, 136.9, 136.5, 136.4, 132.7, 131.3, 128.4, 128.3, 126.5, 122.3, 117.8, 107.1,

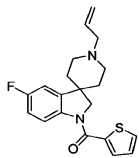
62.4, 51.1, 43.2, 39.1, 37.4, 25.2, 25.1, 21.0, 18.9, 17.9. **HPLC/MS:** Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 3.63 min, ESI^+ = 389.5 (M + H).

5.1.18 Example 18



^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (1H, dd, J = 8.8, 4.8 Hz), 7.44 (2H, s), 6.99 (1H, td, J = 8.8, 2.6 Hz), 6.94 (1H, dd, J = 8.2, 2.6 Hz), 3.60 (2H, s), 3.09 (2H, d, J = 11.8 Hz), 2.26 (2H, d, J = 6.5 Hz), 2.02 (2H, dt, J = 13.1, 3.3 Hz), 1.90 (2H, t, J = 12.1 Hz), 1.73 (2H, d, J = 12.0 Hz), 0.87 (1H, m), 0.54 (2H, m), 0.10 (2H, m). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.21 min, ESI^+ = 469.3 (M + H).

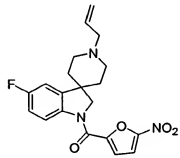
5.1.19 Example 19



^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (1H, m), 7.61 (1H, d, J = 3.4 Hz), 7.58 (1H, d, J = 5.0 Hz), 7.16=5 (1H, dd, J = 4.8, 3.9 Hz), 6.92 (2H, m), 5.90 (1H, ddt, J = 16.9, 13.2, 6.6 Hz), 5.22-5.16 (2H, m), 4.21 (2H, s), 3.04 (2H, d, J = 6.6 Hz), 2.97 (2H, m), 2.05-1.94

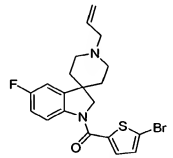
(4H, m), 1.73 (2H, m). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.66 min, ESI^+ = 357.2 (M + H).

5.1.20 Example 20



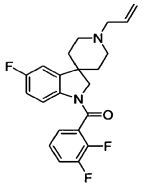
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (1H, m), 7.42 (2H, s), 6.97 (2H, m), 5.92 (1H, ddt, J = 16.7, 13.1, 6.6 Hz), 5.25 (2H, m), 4.44 (2H, s), 3.10-3.04 (4H, m), 2.06 (4H, m), 1.76 (2H, d, J = 12.7 Hz). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.74 min, ESI^+ = 386.1 (M + H).

5.1.21 Example 21



^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (1H, m), 7.37 (1H, d, J = 4.0 Hz), 7.12 (1H, d, J = 4.0 Hz), 6.93 (2H, m), 5.91 (1H, ddt, J = 16.9, 13.3, 6.6 Hz), 5.25 (2H, m), 4.17 (2H, s), 3.09-3.02 (4H, m), 2.03 (4H, m), 1.74 (2H, d, J = 10.8 Hz). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.04 min, ESI^+ = 437.0 (M + H).

5.1.22 Example 22



^{1}H NMR ($CDCl_3$, 400 MHz), A mixture of conformational isomers was evident: δ 8.25 (0.75H, dd, J = 8.8, 4.8 Hz), 7.35-7.21 (3H, m), 6.98 (0.75H, td, J = 8.8, 2.3 Hz), 6.91 (1H, dd, J = 8.2, 2.6 Hz), 6.59 (0.25H, m), 5.92-5.80 (1.25 H, m), 5.30-5.14 (2H, m), 4.38 (0.25H, d, J = 10.7 Hz), 3.95 (0.25H, m), 3.75 (1.5H, s), 3.08 (0.5H, d, J = 6.3Hz), 2.98 (2H, d, J = 6.5 Hz), 2.92 (1.5H, d, J = 11.8 Hz), 2.20-1.80 (4H, m), 1.69 (2H, d, J = 12.5 Hz). **HPLC/MS:** Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.79 min, ESI^+ = 387.3 (M + H).

5.2 Biological Assays

5.2.1 Mas Receptor Agonist Assay

The Mas receptor agonist assay is performed using a mammalian cell line (HEK293) stably expressing the human MAS receptor. For the inverse agonist assay, higher levels of Mas receptor constitutive activity are desired. To achieve this, Mas receptor expression levels are increased by transiently transfecting the same stable cell line with additional human Mas receptor plasmid DNA following standard procedures. These cells are used in the Mas receptor assay approximately 24 hours post-transfection.

Cells are split into 96-well plates (50,000 cells / well) and allowed to attach for a period of 6 hours. The growth medium was then replaced with medium supplemented with 4 μCi/ml [^{3}H]myo-inositol (100ul; Perkin Elmer Life Sciences) and the cells are allowed to incubate for approximately 20 hours. Test compounds are serially diluted in inositol-free media containing 10mM LiCl. The media in the plates is removed by aspiration, replaced with these test compound solutions and incubated at 37°C for 1 hour.

Following this incubation, the media is removed by aspiration and replaced with buffer containing 0.1M formic acid. The plates are then frozen overnight at -80°C to achieve complete cell lysis.

The following day, the assay plates are thawed at room temperature. The thawed contents are then transferred to 96-well filter plates (Millipore, Multiscreen) pre-loaded with resin (Biorad, AG1-X8 100-200 mesh, formate form). The plate is filtered using a vacuum manifold and the resin is washed multiple times with water. An elution buffer is then applied (200ul, 0.2M Ammonium formate / 0.1M formic acid) and the resulting eluent is collected, under vacuum, in a 96-well collection plate. Aliquots of the eluent (80ul) are transferred to filter plates (Whatman, Unifilter GF/C) and dried in a 45°C oven overnight. Dried plates are counted on a scintillation counter following the addition of an appropriate scintillant (Perkin Elmer Life Sciences, Optiphase Supermix or Hi-Safe 3).

5.2.2 Receptor Binding Assay

Mas Receptor Preparation

293 cells (human kidney, ATCC), are transiently transfected with 10 μg human Mas receptor and 60 μl Lipofectamine (per 15-cm dish), grown in the dish for 24 hours (75% confluency) with a media change and removed with 10 ml/dish of Hepes-EDTA buffer (20mM Hepes + 10 mM EDTA, pH 7.4). The cells are then centrifuged in a Beckman Coulter centrifuge for 20 minutes, 17,000 rpm (JA-25.50 rotor). Subsequently, the pellet is resuspended in 20 mM Hepes + 1 mM EDTA, pH 7.4 and homogenized with a 50- ml Dounce homogenizer and again centrifuged. After removing the supernatant, the pellets are stored at -80°C, until used in binding assay. When used in the binding assay, membranes are thawed on ice for about 20 minutes and then 10 mL of incubation buffer (20 mM Hepes, 1 mM $MgCl_2$, 100 mM NaCl, pH 7.4) is added. The membranes are then vortexed to resuspend the crude membrane pellet and homogenized with a Brinkmann PT-3100 Polytron homogenizer for about 15 seconds at setting 6. The concentration of membrane protein is determined using the BRL Bradford protein assay.

Binding Assay

For total binding, a total volume of 50 µl of appropriately diluted membranes (diluted in assay buffer containing 50 mM Tris HCl (pH 7.4), 10 mM $MgCl_2$, and 1 mM EDTA; 5-50 µg protein) is added to 96-well polypropylene microtiter plates followed by addition of 100 µl of assay buffer and 50 µl of a solution of a radio-labeled Compound of the Invention wherein the radio-labeled Compound of the Invention is present at a concnetration of about 1 nM to 1 mM, preferably 1 nM to 500 µM, more preferably 1 nM to 100 µM, more preferably 10 nM to 100 µM, more preferably 100 nM to 100 µM, more preferably 1 µM to 100 µM and most preferably 10 µM to 100 µM. For nonspecific binding, 50 µl of assay buffer is added instead of 100 µl and an additional 50 µl of 10 µM cold Mas is added before 50 µl of a radio-labeled Compound of the Invention is added. Plates are then incubated at room temperature for about 60-120 minutes. The binding reaction is terminated by filtering assay plates through a Microplate Devices GF/C Unifilter filtration plate with a Brandell 96-well plate harvestor followed by washing with cold 50 mM Tris HCl, pH 7.4 containing 0.9% NaCl. The bottom of the filtration plate is then sealed, 50 µl of Optiphase Supermix is added to each well, the top of the filtration plates are sealed, and the filtration plates are counted in a Trilux MicroBeta scintillation counter. For compound competition studies, instead of adding 100 µl of assay buffer, 100 µl of appropriately diluted test compound is added to appropriate wells followed by addition of 50 µl of a radio-labeled Compound of the Invention.

Calculations

The test compounds are initially assayed at 1 and 0.1 µM and then at a range of concentrations chosen such that the middle dose would cause about 50% inhibition of a radio-labeled Compound of the Invention binding (*i.e.*, IC_{50}). Specific binding in the absence of a radio-labeled Compound of the Invention (B_O) is the difference of total binding (B_T) minus non-specific binding (NSB). Similarly, specific binding in the presence of a radio-labeled Compound of the Invention (B) is the difference of displacement binding (B_D) minus non-specific binding (NSB). IC_{50} is determined from an inhibition response curve, logit-log plot of % B/B_O vs concentration of a radio-labeled Compound of the Invention.

K_i is calculated by the Cheng and Prustoff transformation:

$K_i = IC_{50} / (1 + [L]/K_D)$

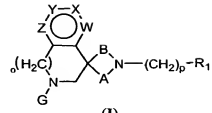
where [L] is the concentration of a radio-labeled Compound of the Invention used in the assay and K_D is the dissociation constant of a radio-labeled Compound of the Invention determined independently under the same binding conditions.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference.

What is claimed is:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, free base, solvate, hydrate or stereoisomer, thereof, wherein:

R_1 is H, halogen, hydroxy, nitro, cyano, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle, substituted or unsubstituted -(5 to 10) membered heteroaryl, $-NR_2R'_2$, $-C(=O)-R_7$, $-S(=O)_2-R_7$;

A is substituted or unsubstituted C_1-C_3 alkylene;

B is substituted or unsubstituted C_1-C_3 alkylene;

G is H, -Ar, $-C(=O)$-Ar, $-C(=O)O$-Ar, $-C(=O)O-C_{1-6}$ alkyl, $-C(=O)N(R_7)$(Ar), $-C(=O)N(R_7)(C_{1-6}$ alkyl), $-S(=O)_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or $-C(=O)C_{1-6}$ alkyl-Ar;

W is N or $-CR_3-$;

X is N or $-CR_4-$;

Y is N or $-CR_5-$;

Z is N or $-CR_6-$;

R_2, R_2', R_3, R_4, R_5, R_6 and R_7 are at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted

or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, -C(=O)-O-C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{0-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{0-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{0-6} alkyl-O-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-NR'-S(=O)$_2$-R', -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$;

o is 0 or 1;

p is 0, 1 or 2;

R' is at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_{3-8} cycloalkyl; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl.

2. A compound of claim 1, wherein W is -CR_3-, X is -CR_4-, Y is -CR_5- and Z is -CR_6-.

3. A compound of claim 1, wherein A and B are both -$(CH_2)_2$-.

4. A compound of claim 1, wherein p is 1 and R_1 is -CH=CH_2.

5. A compound of claim 1, wherein p is 1 and R_1 is -cyclopropyl.

6. A compound of claim 1, wherein R_1 is phenyl.

7. A compound of claim 1, wherein G is -C(=O)-Ar.

8. A compound of claim 1, wherein G is -C(=O)NH-Ar.

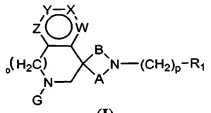
9. A compound of claim 1, wherein G is -$S(=O)_2$-Ar.

10. A compound of claim 1, wherein Ar is phenyl.

11. A compound of claim 1, wherein o is 0.

12. A compound according to claim 1 for use in a method of treatment of the human or animal body by therapy.

13. A method for treating or preventing a cardiovascular disease or disorder comprising administering to a patient in need thereof an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, free base, solvate, hydrate or stereoisomer, thereof, wherein:

R_1 is H, halogen, hydroxy, nitro, cyano, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle, substituted or unsubstituted -(5 to 10) membered heteroaryl, $-NR_2R'_2$, $-C(=O)-R_7$, $-S(=O)_2-R_7$;

A is substituted or unsubstituted C_1-C_3 alkylene;

B is substituted or unsubstituted C_1-C_3 alkylene;

G is H, -Ar, -C(=O)-Ar, -C(=O)O-Ar, -C(=O)O-C_{1-6} alkyl, -C(=O)N(R_7)(Ar), -C(=O)N(R_7)(C_{1-6} alkyl), -S(=O)$_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or -C(=O)C_{1-6} alkyl-Ar;

W is N or -CR_3-;

X is N or -CR_4-;

Y is N or -CR_5-;

Z is N or -CR_6-;

R_2, R_2', R_3, R_4, R_5, R_6 and R_7 are at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, -C(=O)-O-C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{0-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{0-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{0-6} alkyl-O-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-NR'-S(=O)$_2$-R', -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$;

o is 0 or 1;

p is 0, 1 or 2;

R' is at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_{3-8} cycloalkyl; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl.

14. The method of claim 13, wherein W is $-CR_3-$, X is $-CR_4-$, Y is $-CR_5-$ and Z is $-CR_6-$.

15. The method of claim 13, wherein A and B are both $-(CH_2)_2-$.

16. The method of claim 13, wherein p is 1 and R_1 is $-CH=CH_2$.

17. The method of claim 13, wherein p is 1 and R_1 is -cyclopropyl.

18. The method of claim 13, wherein R_1 is phenyl.

19. The method of claim 13, wherein G is -C(=O)-Ar.

20. The method of claim 13, wherein G is -C(=O)NH-Ar.

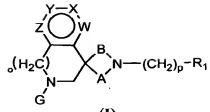
21. The method of claim 13, wherein G is $-S(=O)_2-Ar$.

22. The method of claim 13, wherein Ar is phenyl.

23. The method of claim 13, wherein o is 0.

24. The method of claim 13, wherein the cardiovascular disorder is atherosclerosis, acute myocardial infarction, high blood pressure, primary or secondary hypertension, renal vascular hypertension, acute or chronic congestive heart failure, left ventricular hypertrophy, vascular hypertrophy, glaucoma, primary or secondary hyperaldosteronism, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, renal failure, renal transplant therapy, diabetic retinopathy or migraine.

25. A method for treating or preventing a neurodegenerative disease or disorder comprising administering to a patient in need thereof an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, free base, solvate, hydrate or stereoisomer, thereof, wherein:

R_1 is H, halogen, hydroxy, nitro, cyano, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle, substituted or unsubstituted -(5 to 10) membered heteroaryl, $-NR_2R'_2$, $-C(=O)-R_7$, $-S(=O)_2-R_7$;

A is substituted or unsubstituted C_1-C_3 alkylene;

B is substituted or unsubstituted C_1-C_3 alkylene;

G is H, -Ar, $-C(=O)$-Ar, $-C(=O)O$-Ar, $-C(=O)O-C_{1-6}$ alkyl, $-C(=O)N(R_7)$(Ar), $-C(=O)N(R_7)(C_{1-6}$ alkyl), $-S(=O)_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or $-C(=O)C_{1-6}$ alkyl-Ar;

W is N or $-CR_3-$;

X is N or $-CR_4-$;

Y is N or $-CR_5-$;

Z is N or $-CR_6-$;

R_2, R_2', R_3, R_4, R_5, R_6 and R_7 are at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, $-C(=O)-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-$O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-NH_2, $-C_{0-6}$ alkyl-$C(=O)-NH(C_{1-6}$ alkyl), $-C_{0-6}$ alkyl-$C(=O)-N(C_{1-6}$ alkyl)(C_{1-6} alkyl), $-C_{1-6}$ alkyl-$NH-C(=O)-C_{1-6}$ alkyl, $-C_{1-6}$

alkyl-S(=O)-C_{1-6} alkyl, -C_{0-6} alkyl-O-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-NR'-S(=O)$_2$-R', -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -$(C(R')_2)_{0-6}$-O-$(C(R')_2)_{1-5}C(R')_3$, -$(C(R')_2)_{1-5}C(R')_3$, -$(C(R')_2)_{0-6}$-S-$(C(R')_2)_{1-5}C(R')_3$, -$(C(R')_2)_{0-6}$-S(=O)-$(C(R')_2)_{1-5}C(R')_3$ or -$(C(R')_2)_{0-6}$-S(=O)$_2$-$(C(R')_2)_{1-5}C(R')_3$;

o is 0 or 1;

p is 0, 1 or 2;

R' is at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_{3-8} cycloalkyl; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl.

26. The method of claim 25, wherein W is -CR_3-, X is -CR_4-, Y is -CR_5- and Z is -CR_6-.

27. The method of claim 25, wherein A and B are both -$(CH_2)_2$-.

28. The method of claim 25, wherein p is 0 and $R_1$is -CH=CH_2-.

29. The method of claim 25, wherein p is 0 and $R_1$is -cyclopropyl.

30. The method of claim 25, wherein $R_1$is phenyl.

31. The method of claim 25, wherein G is -C(=O)-Ar.

32. The method of claim 25, wherein G is -C(=O)NH-Ar.

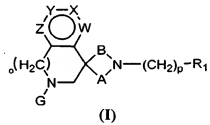
33. The method of claim 25, wherein G is -S(=O)$_2$-Ar.

34. The method of claim 25, wherein Ar is phenyl.

35. The method of claim 25, wherein 0 is 0.

36. The method of claim 25, wherein the neurodegenerative disease or disorder is diabetic peripheral neuropathy, stroke, cerebral ischemia or Parkinson's disease.

37. A method for treating or preventing a disorder treatable or preventable by inhibiting Mas receptor function, comprising administering a patient in need thereof an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, free base, solvate, hydrate or stereoisomer, thereof, wherein:

R_1 is H, halogen, hydroxy, nitro, cyano, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle, substituted or unsubstituted -(5 to 10) membered heteroaryl, $-NR_2R'_2$, $-C(=O)-R_7$, $-S(=O)_2-R_7$;

A is substituted or unsubstituted C_1-C_3 alkylene;

B is substituted or unsubstituted C_1-C_3 alkylene;

G is H, -Ar, $-C(=O)$-Ar, $-C(=O)O$-Ar, $-C(=O)O-C_{1-6}$ alkyl, $-C(=O)N(R_7)$(Ar), $-C(=O)N(R_7)(C_{1-6}$ alkyl), $-S(=O)_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or $-C(=O)C_{1-6}$ alkyl-Ar;

W is N or $-CR_3-$;

X is N or $-CR_4-$;

Y is N or -CR_5-;

Z is N or -CR_6-;

R_2, R_2', R_3, R_4, R_5, R_6 and R_7 are at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, -C(=O)-O-C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{0-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{0-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{0-6} alkyl-O-S(=$O)_2$-C_{1-6} alkyl, -C_{1-6} alkyl-S(=$O)_2$-C_{1-6} alkyl, -C_{1-6} alkyl-NR'-S(=$O)_2$-R', -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -$(C(R')_2)_{0-6}$-O-$(C(R')_2)_{1-5}C(R')_3$, -$(C(R')_2)_{1-5}C(R')_3$, -$(C(R')_2)_{0-6}$-S-$(C(R')_2)_{1-5}C(R')_3$, -$(C(R')_2)_{0-6}$-S(=O)-$(C(R')_2)_{1-5}C(R')_3$ or -$(C(R')_2)_{0-6}$-S(=$O)_2$-$(C(R')_2)_{1-5}C(R')_3$;

o is 0 or 1;

p is 0, 1 or 2;

R' is at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_{3-8} cycloalkyl; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl.

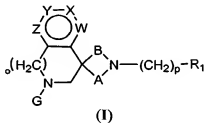
38. The method of claim 37, wherein the disease or disorder is a cardiovascular disease or disorder.

39. The method of claim 38, wherein the cardiovascular disease or disorder is atherosclerosis, acute myocardial infarction, high blood pressure, primary or secondary hypertension, renal vascular hypertension, acute or chronic congestive heart failure, left ventricular hypertrophy, vascular hypertrophy, glaucoma, primary or secondary hyperaldosteronism, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, renal failure, renal transplant therapy, diabetic retinopathy or migraine.

40. The method of claim 37, wherein the disease or disorder is a neurodegenerative disease or disorder.

41. The method of claim 40, wherein the neurodegenerative disease or disorder is diabetic peripheral neuropathy, stroke, cerebral ischemia or Parkinson's disease.

42. A method for inhibiting Mas receptor function in a cell, comprising contacting a cell capable of expressing Mas with an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, free base, solvate, hydrate or stereoisomer, thereof, wherein:

R_1 is H, halogen, hydroxy, nitro, cyano, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle, substituted or unsubstituted -(5 to 10) membered heteroaryl, $-NR_2R'_2$, $-C(=O)-R_7$, $-S(=O)_2-R_7$;

A is substituted or unsubstituted C_1-C_3 alkylene;

B is substituted or unsubstituted C_1-C_3 alkylene;

G is H, -Ar, -C(=O)-Ar, -C(=O)O-Ar, -C(=O)O-C_{1-6} alkyl, -C(=O)N(R_7)(Ar), -C(=O)N(R_7)(C_{1-6} alkyl), -S(=O)$_2$-Ar, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-Ar or -C(=O)C_{1-6} alkyl-Ar;

W is N or -CR_3-;

X is N or -CR_4-;

Y is N or -CR_5-;

Z is N or -CR_6-;

R_2, R_2', R_3, R_4, R_5, R_6 and R_7 are at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted aryl, -C(=O)-O-C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{0-6} alkyl-C(=O)-NH(C_{1-6} alkyl), -C_{0-6} alkyl-C(=O)-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-NH-C(=O)-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)-C_{1-6} alkyl, -C_{0-6} alkyl-O-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-S(=O)$_2$-C_{1-6} alkyl, -C_{1-6} alkyl-NR'-S(=O)$_2$-R', -C_{1-6} alkyl-SH, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=S)-NH-C_{1-6} alkyl, -C_{1-6} alkyl-NH-C(=O)-NH-C_{1-6} alkyl, -C_{0-6} alkyl-N(R')$_2$, -C_{0-6} alkyl-NHOH, -C_{0-6} alkyl-C(=O)O-C_{1-6} alkyl, -(C(R')$_2$)$_{0-6}$-O-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S-(C(R')$_2$)$_{1-5}$C(R')$_3$, -(C(R')$_2$)$_{0-6}$-S(=O)-(C(R')$_2$)$_{1-5}$C(R')$_3$ or -(C(R')$_2$)$_{0-6}$-S(=O)$_2$-(C(R')$_2$)$_{1-5}$C(R')$_3$;

o is 0 or 1;

p is 0, 1 or 2;

R' is at each occurrence independently H, halogen, hydroxy, amino, cyano, nitro, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_{3-8} cycloalkyl; and

Ar is substituted or unsubstituted aryl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{8-14} bicycloalkyl, substituted or unsubstituted C_{8-14} tricycloalkyl, substituted or unsubstituted -(3 to 7) membered heterocycle, substituted or unsubstituted -(7 to 10) membered bicycloheterocycle or substituted or unsubstituted -(5 to 10 membered)heteroaryl.

43. A composition comprising a compound, or a pharmaceutically acceptable salt of a compound, of claim 1 and a pharmaceutically acceptable vehicle or excipient.

44. A method for the manufacture of a medicament comprising a compound of claim 1, for use in the treatment of a cardiovascular disease.

45. A method for the manufacture of a medicament comprising a compound of claim 1, for use in the treatment of a neurodegenerative disease.

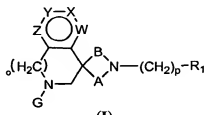
46. A method for the manufacture of a medicament comprising a compound of claim 1, for use as a neuro-protective agent.

47. A method for the manufacture of a medicament comprising a compound of claim 1, for use as a cardio-protective agent.

48. **ABSTRACT**

NOVEL COMPOUNDS OF THE INVENTION, METHODS OF USE THEREWITH AND COMPOSITIONS THEREOF

The invention provides compounds of Formula (I):



(I)

and pharmaceutically acceptable salts, solvates and stereoisomers thereof, wherein A, B, G, W, X, Y, Z, o, p and R_1 are as disclosed herein ("Compound(s) of the Invention"), which are useful as cardio-protective and/or neuro-protective agents. The invention also provides pharmaceutical compositions comprising a Compound of the Invention and methods for treating, preventing and/or managing a cardiovascular or neurodegenerative disease or disorder, comprising administering to a patient in need thereof a Compound of the Invention.